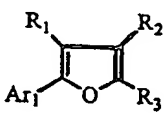




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA98/00930 <b>(22) International Filing Date:</b> 1 October 1998 (01.10.98) <b>(30) Priority Data:</b> 60/061,261 3 October 1997 (03.10.97) US <b>(71) Applicant (for all designated States except US):</b> MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> PERRIER, Helene [CA/CA]; (CA). HAN, Yongxin [CA/CA]; (CA). BAYLY, Christopher [CA/CA]; (CA). MacDONALD, Dwight [CA/CA]; (CA). GIROUX, Andre [CA/CA]; (CA). YOUNG, Robert, N. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). <b>(74) Agent:</b> MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA).	<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> With international search report. With amended claims.	
<b>(54) Title:</b> ARYL FURAN DERIVATIVES AS PDE IV INHIBITORS		
<div style="text-align: center;"><span style="margin-left: 20px;">(I)</span></div>		
<b>(57) Abstract</b> <p>The invention encompasses the novel compound of Formula (I) useful in the treatment of diseases, including asthma, by raising the level of cyclic adenosine-3',5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE IV). The invention also encompasses certain pharmaceutical compositions and methods for treatment of diseases by inhibition of PDE IV, resulting in an elevation of cAMP, comprising the use of compounds of Formula (I).</p>		

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## TITLE OF THE INVENTION

ARYL FURAN DERIVATIVES AS *PDE IV* INHIBITORS

## 5 BACKGROUND OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions for the treatment of diseases by raising the level of cyclic adenosine-3',5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (*PDE IV*).

10 Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of 3', 5'-cyclic adenosine monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by  
15 agents such as forskolin or indirectly activated by the binding of specific agonists to cell surface receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (*PDE*) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family  
20 have been described (*PDE I-VII*) the distribution of which varies from tissue to tissue. This suggests that specific inhibitors of *PDE* isoenzymes could achieve differential elevation of cAMP in different tissues, [for reviews of *PDE* distribution, structure, function and regulation, see Beavo & Reifsnnyder (1990) *TIPS*, 11: 150-155 and Nicholson et al (1991)  
25 *TIPS*, 12: 19-27].

The availability of *PDE* isotype selective inhibitors has enabled the role of *PDEs* in a variety of cell types to be investigated. In particular it has been established that *PDE IV* controls the breakdown of cAMP in many inflammatory cells, for example, basophils (Peachell  
30 P.T. et al., (1992) *J. Immunol.* 148 2503-2510) and eosinophils (Dent G. et al., (1991) *Br. J. Pharmacol.* 103 1339-1346) and that inhibition of this isotype is associated with the inhibition of cell activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. Consequently *PDE IV* inhibitors are currently being developed as  
35 potential anti-inflammatory drugs particularly for the prophylaxis and

treatment of asthma, by achieving both anti-inflammatory and bronchodilator effects.

The application of molecular cloning to the study of PDEs has revealed that for each isotype there may be one or more isoforms.

- 5 For PDE IV, it has been shown that there are four isoforms (A, B, C and D) each coded for by a separate gene in both rodents (Swinnen J.V. *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86 5325-5329) and man (Bolger G. *et al.*, (1993) *Mol. Cell Biol.* 13 6558-6571).

- 10 The existence of multiple PDE IVs raises the prospect of obtaining inhibitors that are selective for individual isoforms, thus increasing the specificity of action of such inhibitors. This assumes that the different PDE IV isoforms are functionally distinct. Indirect evidence in support of this comes from the selective distribution of these isoforms in different tissues (Swinnen *et al.*, 1989; Bolger *et al.*, 1993; 15 Obernolte R. *et al.*, (1993) *Gene* 129 239-247, *ibid*) and the high degree of sequence conservation amongst isoforms of different species.

- To date full length cDNAs for human PDE IVA, B and D (Bolger *et al.*, 1993 *ibid*; Obernolte *et al.*, 1993 *ibid*; McLaughlin M. *et al.*, (1993) *J. Biol. Chem.* 268 6470-6476) and rat PDE IVA, B and D (Davis R. 20 *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86 3604-3608; Swinnen J.V. *et al.*, (1991) *J. Biol. Chem.* 266 18370-18377), have been reported, enabling functional recombinant enzymes to be produced by expression of the cDNAs in an appropriate host cell. These cDNAs have been isolated by conventional hybridisation methods. However using this approach, only 25 partial cDNAs for both human and rat PDE IVC have been obtained. (Bolger *et al.*, *ibid.* 1993 and Swinnen *et al.*, *ibid.* 1989 and International Patent Specification No. WO 91/16457.)

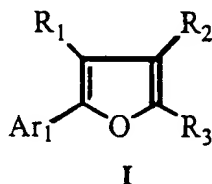
- 30 The design of PDE IV inhibitors for the treatment of inflammatory diseases such as asthma, has met with limited success to date. Many of the PDE IV inhibitors which have been synthesised have lacked potency and/or inhibit more than one type of PDE isoenzyme in a non-selective manner. PDE IV inhibitors that are relatively potent and selective for PDE IV, are reported to be emetic as well. Indeed this side effect has been so universal that experts have expressed their belief that

the emesis experienced upon administration of a PDE IV inhibitor, may be mechanism based.

We have now found a novel series of aryl furan derivatives, members of which compared to known structurally similar compounds are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs. Advantageously, compounds according to the invention have good oral activity and at orally effective doses exhibit little or none of the side-effects associated with known PDE IV inhibitors, such as rolipram. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma and other inflammatory conditions.

#### SUMMARY OF THE INVENTION

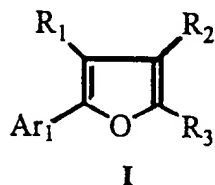
The invention encompasses novel compounds of Formula I useful in the treatment of disease by inhibition of PDE IV, resulting in an elevation of cAMP.



The invention also encompasses certain pharmaceutical compositions and methods for treatment of diseases by inhibition of PDE IV, resulting in an elevation of cAMP, comprising the use of compounds of Formula I.

#### DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I useful in the treatment of disease by inhibition of PDE IV, resulting in an elevation of cAMP,



5

or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> is an aromatic ring selected from phenyl, pyridinyl or furyl, optionally substituted with up to two substituents selected independently from among:

- a) C<sub>1-6</sub>alkyl, optionally substituted with -OH, -CO<sub>2</sub>H, CO<sub>2</sub>C<sub>1-3</sub>alkyl, and CN,
- b) C<sub>1-6</sub>alkoxy,
- c) C<sub>1-3</sub>alkylthio,
- d) C<sub>1-3</sub>alkylsulfonyl,
- e) C<sub>1-3</sub>fluoroalkyl, optionally substituted with -OH,
- f) halo,
- g) -OH,
- h) -CO<sub>2</sub>H,
- i) -CO<sub>2</sub>C<sub>1-3</sub>alkyl,

15

20

R<sup>1</sup> is selected from:

- a) hydrogen,
- b) halo,
- c) C<sub>1-C<sub>6</sub></sub>alkylcarbonyloxy,
- d) C<sub>1-3</sub>alkyl, optionally substituted with -OH, N-C<sub>1-4</sub>alkyl, cyclo-N-C<sub>5-7</sub>alkyl, piperazine, C<sub>1-4</sub>alkylcarbonylpiperazine, morpholine or hydroxypiperidine,
- e) C<sub>1-4</sub>alkylcarbonyl,
- f) tri(C<sub>1-3</sub>alkyl)silyl,
- g) N-morpholinyl or

25

30

h)-X-Y-Ar<sup>2</sup>,

wherein:

X is 1) -CH<sub>2</sub>-,  
2) -CO-, or  
3) a bond;

Y is 1) -O-,  
2) -S-,  
3) -S(O)<sub>2</sub>-,  
4) -NR<sup>4</sup>-, or  
5) a bond;

Ar<sup>2</sup> is an aromatic ring selected from phenyl, benzothiazolyl, benzoxazolyl, pyrimidinyl, pyridinyl, purinyl or imidazolyl optionally substituted with up to two substituents selected independently among:

1) C<sub>1-6</sub>alkyl,  
2) C<sub>1-6</sub>alkoxy,  
3) -OH,  
4) halo, or  
5) CF<sub>3</sub>;

R<sup>2</sup> is selected from:

a) hydrogen or  
b) C<sub>1-3</sub>alkyl.

R<sup>3</sup> is selected from phenyl, pyridinyl, quinolinyl or furyl, optionally substituted with up to two substituents chosen independently among:

a) C<sub>1-3</sub>alkyl,  
b) C<sub>1-3</sub>fluoroalkyl,  
c) C<sub>1-6</sub>alkoxy,  
d) C<sub>1-3</sub>fluoroalkoxy,  
e) C<sub>1-3</sub>alkylthio,  
f) halo, or  
g) -OH, and

R<sup>4</sup> is chosen from among:

- a) hydrogen, or
- b) C<sub>1-5</sub>alkyl.

5        Within this embodiment there is a preferred genus of  
compounds wherein  
R<sup>2</sup> is hydrogen;  
and all other variables are defined as in Formula I above.

10       Another preferred genus is that in which -X-Y- is -CH<sub>2</sub>-S-  
and all other variables are as described above.

Another preferred genus is that in which Ar<sup>2</sup> is  
pyrimidinyl, optionally substituted with up to two substituents chosen  
independently among:  
15                    1) C<sub>1-6</sub>alkyl,  
                      2) C<sub>1-6</sub>alkoxy,  
                      3) -OH, or  
                      4) halo.

20       Still another preferred genus is realized when:  
Ar<sup>1</sup> is an aromatic ring selected from phenyl, pyridinyl or furyl,  
optionally substituted with up to two substituents selected independently  
from among:  
25                    a) C<sub>1-6</sub>alkyl, optionally substituted with -OH, -CO<sub>2</sub>H, CO<sub>2</sub>C<sub>1-3</sub>  
                      3alkyl, and CN,  
                      b) C<sub>1-6</sub>alkoxy,  
                      c) C<sub>1-3</sub>alkylthio,  
                      d) C<sub>1-3</sub>alkylsulfonyl,  
                      e) C<sub>1-3</sub>fluoroalkyl, optionally substituted with -OH,  
30                    f) halo,  
                      g) -OH,  
                      h) -CO<sub>2</sub>H,  
                      i) -CO<sub>2</sub>C<sub>1-3</sub>alkyl,

35       R<sup>1</sup> is selected from:



- a) hydrogen,
- b) halo,
- c) C<sub>1-3</sub> alkyl, optionally substituted with OH,
- h) -X-Y-Ar<sup>2</sup>,

5    wherein:

- X is
- 1) -CH<sub>2</sub>-,
  - 2) -CO-, or
  - 3) a bond;
- Y is
- 1) -O-,
  - 10    2) -S-,
  - 3) -S(O)<sub>2</sub>-,
  - 4) -NR<sup>4</sup>-, or
  - 5) a bond;

15    Ar<sup>2</sup> is an aromatic ring selected from phenyl, pyrimidinyl, pyridinyl, purinyl or imidazolyl optionally substituted with up to two substituents selected independently among:

- 1) C<sub>1-6</sub>alkyl,
- 2) C<sub>1-6</sub>alkoxy,
- 3) -OH,
- 20    4) halo, or

R<sup>2</sup> is selected from:

- a) hydrogen or
- b) C<sub>1-3</sub>alkyl.

25    R<sup>3</sup> is selected from phenyl, pyridinyl, or quinolinyl, optionally substituted with up to two substituents chosen independently among:

- a) C<sub>1-3</sub>alkyl,
- b) C<sub>1-3</sub>fluoroalkyl,
- c) C<sub>1-6</sub>alkoxy,
- 30    d) C<sub>1-3</sub>fluoroalkoxy,
- e) C<sub>1-3</sub>alkylthio,
- f) halo, or
- g) -OH, and

35    R<sup>4</sup> is chosen from among:

- a) hydrogen, or
- b) C<sub>1-5</sub>alkyl.

As appreciated by those of skill in the art, halo is intended to include F, Cl, Br, and I.

5

For purposes of this specification alkyl is defined to include straight, branched, and cyclic structures of the indicated number of carbon atoms. By way of example, C<sub>1-6</sub>alkyl includes methyl, ethyl, propyl, i-propyl, s- and t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl and alkylcarbonyl mean the corresponding groups of the indicated number of carbon atoms of a straight, branched, or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -SCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. Fluoroalkyl means an alkyl group of the indicated number of carbon atoms, of straight, branched or cyclic structure, in which one or more hydrogen atoms have been replaced by fluorine atoms; fluoroalkoxy, fluoroalkylthio, fluoroalkylsulfinyl, and fluoroalkylsulfonyl have the analogous meanings.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for treatment of disease by inhibition of PDE IV, as disclosed herein comprising a pharmaceutically acceptable

carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for treatment of disease by inhibition of PDE IV, resulting in an elevation of cAMP, as disclosed herein  
5 comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

For purposes of this specification a compound is said to  
10 selectively inhibit PDE IV in preference to other PDE's if the ratio of the IC50 concentration for all other PDE inhibition to PDE IV inhibition is 100 or greater.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a  
15 pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from  
20 inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases  
25 include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine,  
30 glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

5 Compounds according to the invention are selective and potent inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

10 The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human diseases where an unwanted inflammatory response or muscular spasm (for example bladder or alimentary smooth muscle spasm) is present and where the elevation of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

15 Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative  
20 colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes, alzheimers disease, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and atherosclerosis.

25 Compounds of the invention also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

30 Compounds according to the invention may also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, transplant rejection and graft versus host disease.

35 Compounds of the invention suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation.

They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention suppress inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention ameliorate these symptoms with a consequent enhancement of quality of life.

Compounds of the invention also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

Compounds of the invention suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of Formula I together with one or more pharmaceutically acceptable carriers, excipients or diluents.

For the treatment of any of these, compounds of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or

granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents  
5 selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.  
10 These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate,  
15 stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be  
20 coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or  
25 kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous  
30 suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation  
35 products of an alkylene oxide with fatty acids, for example

polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example

polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such  
5 formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents  
10 which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride  
15 solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the  
20 form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

25 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)



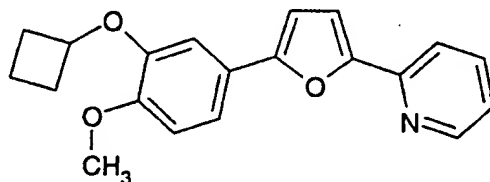
Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the  
5 administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary  
10 depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total  
15 composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level  
20 for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

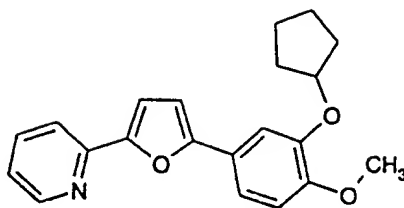
Exemplifying the invention are:

Example 1



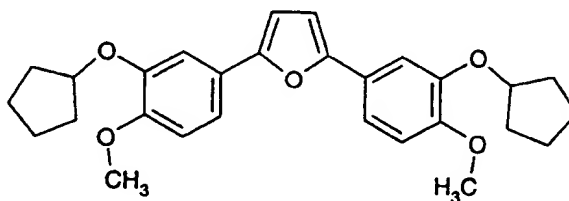
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.55 (d, 1H), 7.85 (dd, 2H), 7.42 (dd, 1H), 7.28 (d, 1H), 7.22 (m, 1H), 7.13 (d, 1H), 7.05 (d, 1H), 6.85 (d, 1H), 4.80  
30 (m, 1H), 3.85 (s, 3H), 2.51 (m, 2H), 2.18 (m, 2H), 1.85 (q, 1H), 1.70 (q, 1H).

## Example 2



Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.53 (d, 1H), 7.84 (m, 2H), 7.42 (m, 2H), 7.23 (m, 1H), 7.17 (d, 1H), 7.03 (d, 1H), 6.96 (d, 1H), 4.95 (m, 1H), 3.84 (s, 3H), 1.98-1.78 (m, 6H), 1.65 (m, 2H).

## Example 3

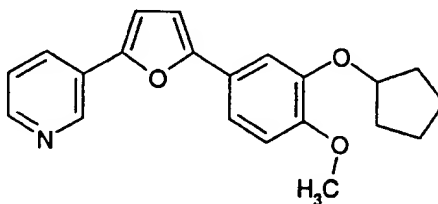


10

Proton NMR (300MHz, acetone-d<sub>6</sub>): 7.48 (s, 1H), 7.45 (d, 1H), 7.0 (d, 1H), 6.75 (s, 1H), 4.95 (m, 1H), 3.8 (s, 3H), 1.98-1.75 (m, 6H), 1.65 (m, 2H).

15

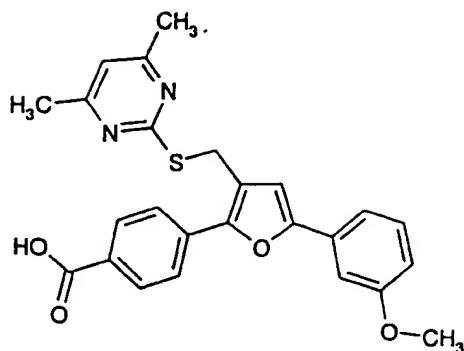
## Example 4



20

Proton NMR (300MHz, acetone-d<sub>6</sub>): 9.05 (s, 1H), 8.48(dd, 1H), 8.1 (dd, 1H), 7.4 (m, 3H), 7.05(dd, 1H), 7.05(dd, 1H), 7.00 (dd, 1H), 6.85 (dd, 1H), 4.95 (m, 1H), 3.80 (s, 3H), 1.98-1.75 (m, 6H), 1.60(m, 2H).

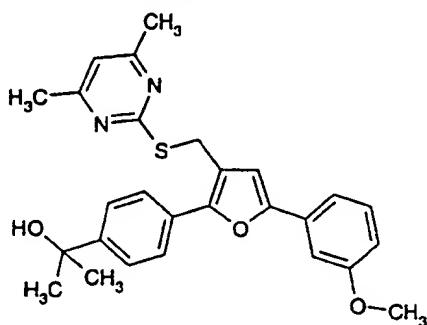
## Example 5



Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.16 (d, 2H), 8.00 (d, 2H), 7.40-7.30 (m, 3H), 7.10 (s, 1H), 6.90 (m, 2H), 4.59 (s, 2H), 3.88 (s, 3H), 2.30 (s, 6H).

5

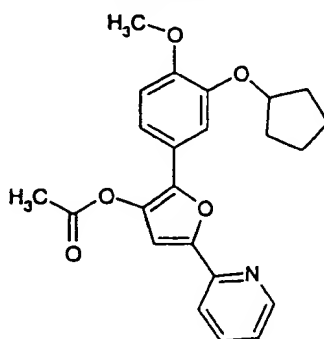
### Example 6



Proton NMR (400MHz, acetone-d<sub>6</sub>): 7.80 (d, 2H), 7.65 (d, 2H), 7.38-7.28 (m, 3H), 7.06 (s, 1H), 6.89 (s, 1H), 6.88 (m, 1H), 4.53 (s, 2H), 3.87 (s, 3H), 2.35 (s, 6H), 1.56 (s, 6H).

10

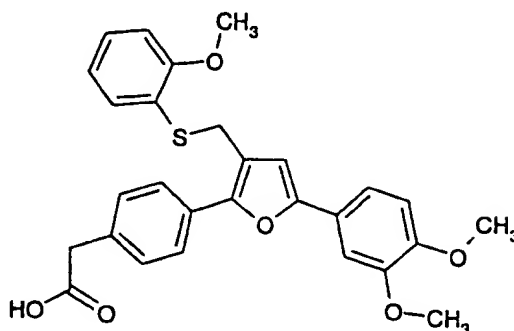
### Example 7



Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.58 (d, 1H), , 7.7 (bs, 2H), 7.35 (dd, 2H), 7.25(s, 1H), 7.10(m, 1H), 6.91(dd, 1H), 4.82 (m, 1H), 3.88 (s, 3H), 2.3(s, 3H), 1.98-1.75 (m, 6H), 1.60(m, 2H).

5

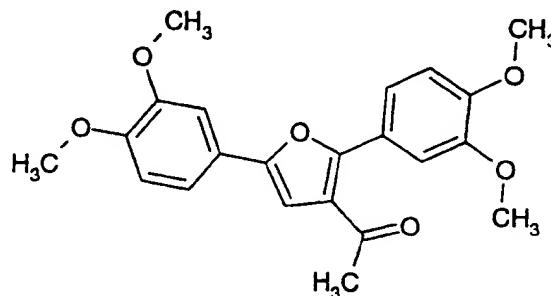
## Example 8



Proton NMR (400MHz, acetone-d<sub>6</sub>): 7.73 (d, 2H), 7.41 (d, 2H), 7.39-7.28 (m, 2H), 7.21-7.14 (m, 1H), 7.00-6.87 (m, 3H), 6.86 (s, 1H), 6.75 (d, 1H), 4.33 (s, 2H), 3.89 (s, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H).

10

## Example 9

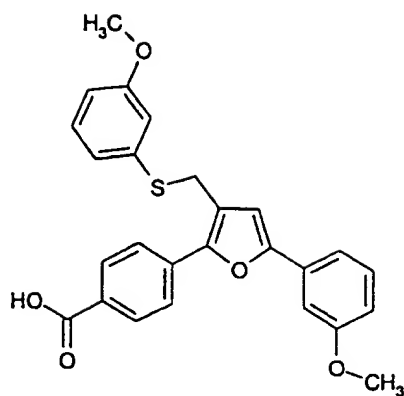


15

Proton NMR (300MHz, acetone-d<sub>6</sub>): 7.78 (s, 1H), 7.55 (dd, 2H), 7.3 (dd, 2H), 7.15 (s, 1H) 6.9 (m, 1H), 3.95 (m, 12H), 2.45 (s, 3H).

20

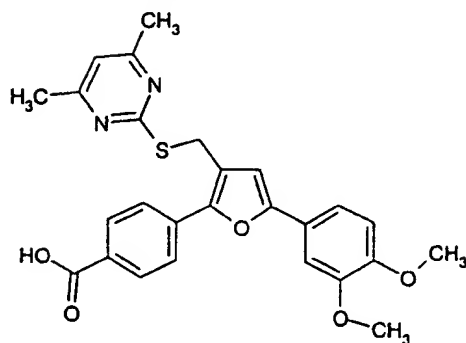
## Example 10



HPLC-MS: 445.3 (M-1).

5

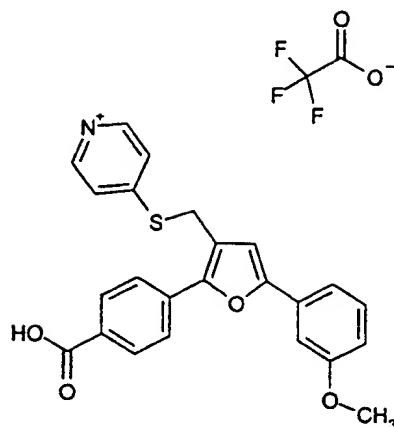
### Example 11



Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.14 (d, 2H), 7.98 (d, 2H), 7.38 (m, 2H), 7.03 (d, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 4.58 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.32 (s, 6H).

10

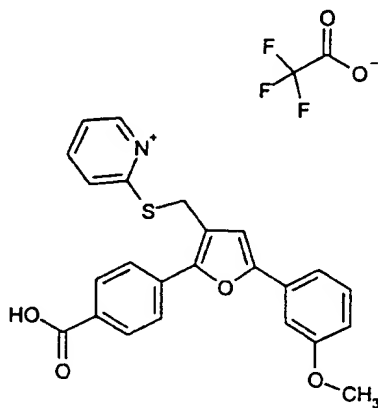
### Example 12



Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.70 (d, 1H), 8.14 (d, 2H), 7.99 (d, 2H), 7.84 (d, 2H), 7.45-7.35 (m, 3H), 7.18 (s, 1H), 6.90 (m, 1H), 4.83 (s, 2H), 3.86 (s, 3H).

5

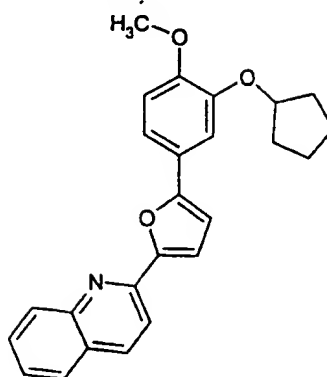
### Example 13



Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.45 (dm, 1H), 8.14 (d, 2H), 7.99 (d, 2H), 7.63 (m, 1H), 7.45-7.28 (m, 4H), 7.12 (m, 1H), 7.10 (s, 1H), 6.90 (m, 1H), 4.63 (s, 2H), 3.86 (s, 3H).

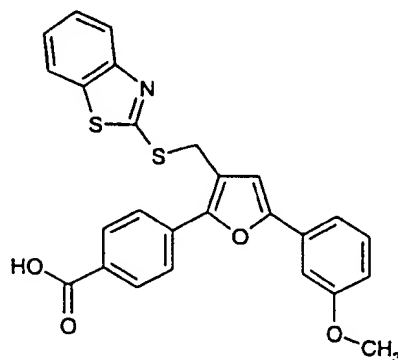
10

## Example 14



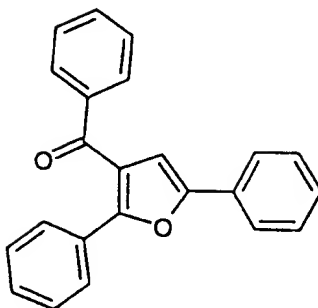
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.38 (d, 1H), 8.1 (d, 1H), 8.05 (d, 1H)  
 7.95 (d, 1H), 7.75 (t, 1H), 7.5 (m, 3H), 7.38 (d, 1H), 7.1 (d, 1H), 6.95 (d, 1H),  
 5.0 (m, 1H), 3.85 (s, 3H), 1.95-1.8 (m, 6H), 1.60 (m, 2H).

## Example 15



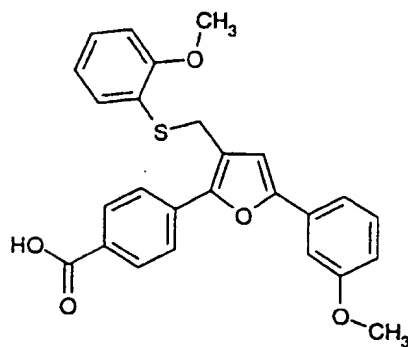
Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.16 (d, 2H), 8.02 (d, 2H), 7.92 (d, 1H),  
 7.82 (d, 1H), 7.50-7.30 (m, 5H), 7.19 (s, 1H), 6.90 (m, 1H), 4.86 (s, 2H), 3.85  
 (s, 3H).

## Example 16



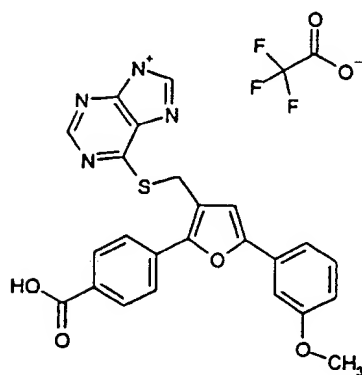
5

## Example 17



HPLC-MS: 445.3 (M-1).

## Example 18

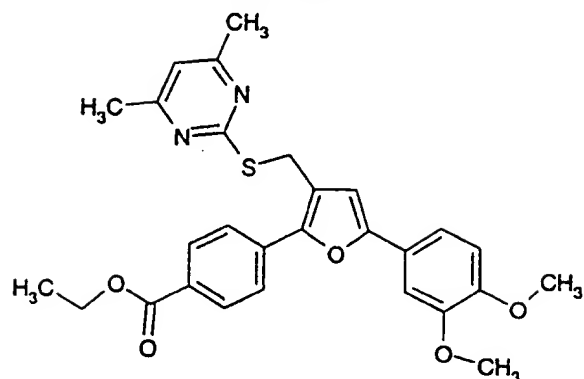


10

HPLC-MS: 457.1 (M-1).

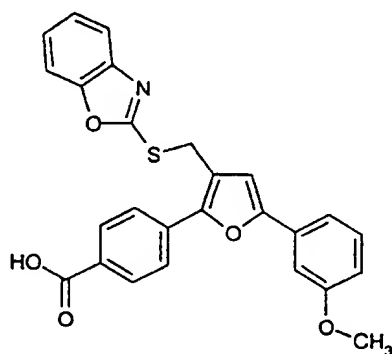


## Example 19



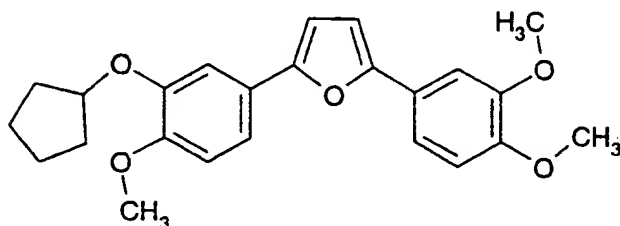
Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.20 (d, 2H), 7.94 (d, 2H), 7.38-7.35 (m, 2H), 7.03 (d, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 4.56 (s, 2H), 4.36 (q, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.32 (s, 6H), 1.37 (t, 3H).

## Example 20



10

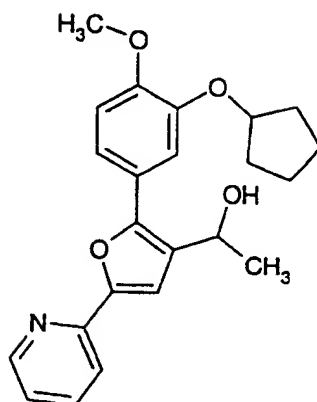
## Example 21



Proton NMR (300MHz, acetone-d<sub>6</sub>): 7.3 (dd, 2H), 6.9 (dd, 2H), 7.0 (d, 1H), 6.5 (d, 2H), 4.85 (t, 1H), 4.0 (s, 3H), 3.95 (s, 3H), 1.9-1.6 (m, 8H).

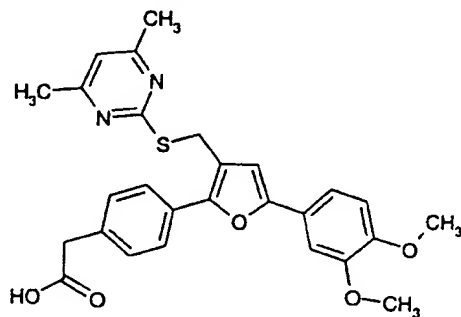
15

## Example 22



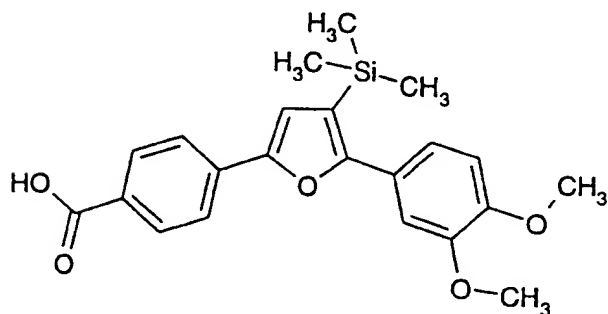
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.55 (d, 1H), 7.82 (m, 2H), 7.47 (s, 1H), 7.36 (d, 1H), 7.28 (s, 1H), 7.21 (d, 1H), 7.12 (m, 1H), 5.05 (m, 1H) 4.9 (m, 1H),  
 5 3.85 (s, 3H), 1.95-1.75 (m, 6H), 1.7 (m, 2H) 1.55 (dd, 3H).

## Example 23

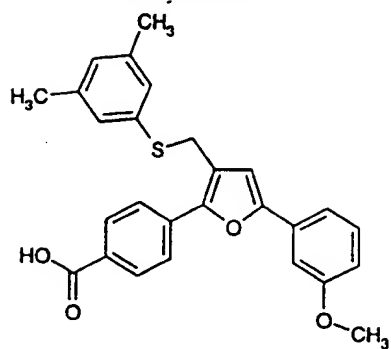


10

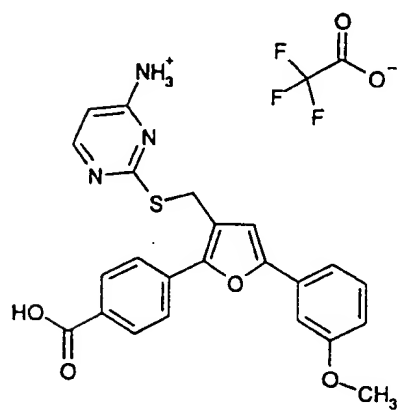
## Example 24



## Example 25



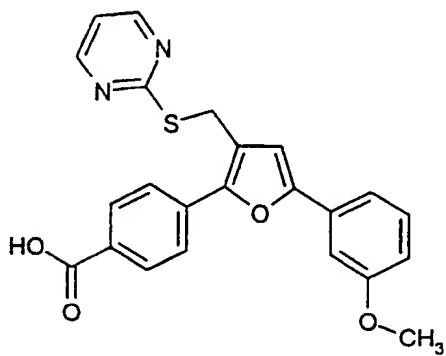
## Example 26



5

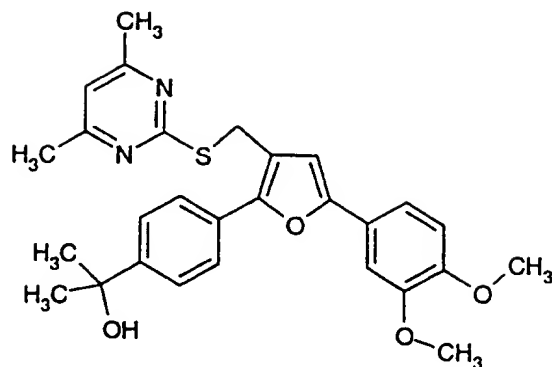
HPLC-MS: 432.3 (M-1).

## Example 27



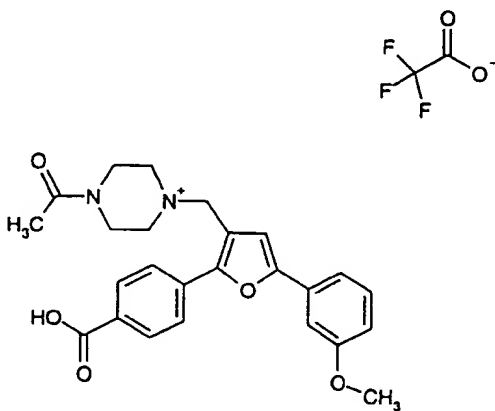
10 HPLC-MS: 417.2 (M-1).

## Example 28



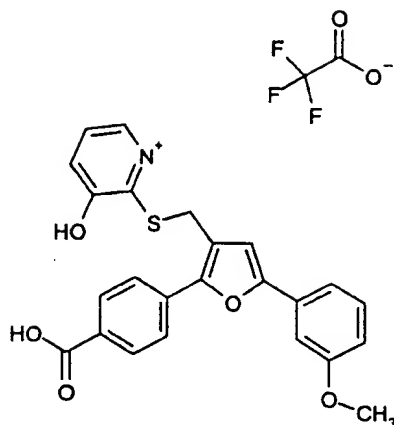
Proton NMR (400MHz, acetone-d<sub>6</sub>): 7.77 (d, 2H), 7.64 (d, 2H), 7.35-7.32 (m, 2H), 7.00 (d, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 4.51 (s, 2H), 3.88(s, 3H), 3.83 (s, 3H), 2.32 (s, 6H), 1.54 (s, 6H).

## Example 29

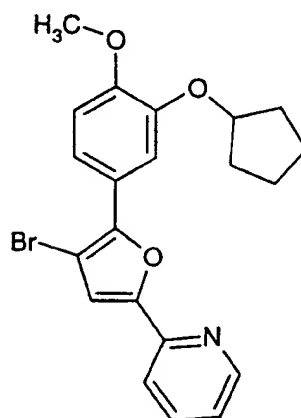


Proton NMR (400MHz, acetone-d<sub>6</sub>): 8.13 (d, 2H), 7.96 (d, 2H), 7.46 (s, 1H), 7.39-7.34 (m, 3H), 6.93 (m, 1H), 4.69 (s, 2H), 3.90 (bd, 4H), 3.87 (s, 3H), 3.42 (bd, 4H), 2.08 (s, 3H).

## Example 30



## Example 31

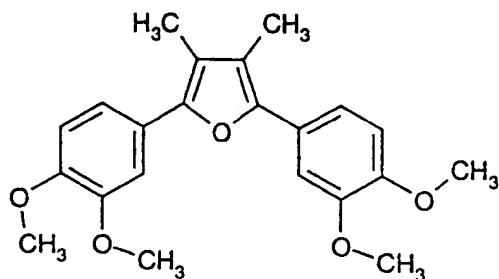


5

Proton NMR (300MHz, acetone- $d_6$ ): 8.50 (d, 1H), 7.85 (m, 2H), 7.43 (m, 2H), 7.23 (m, 2H), 7.05 (dd, 1H), 4.95 (m, 1H), 3.90 (s, 3H), 1.98-1.80 (m, 6H), 1.65 (m, 2H).

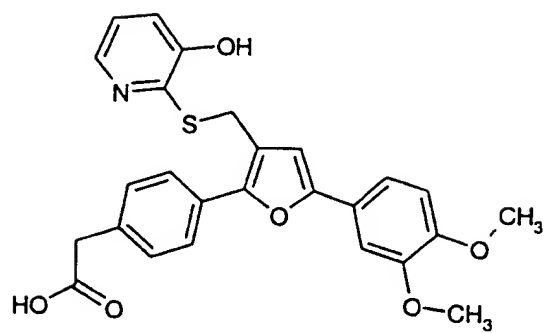
10

## Example 32

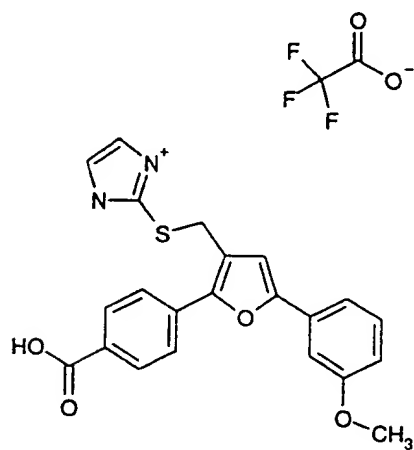


HPLC MS: 309 (M+1)

## Example 33

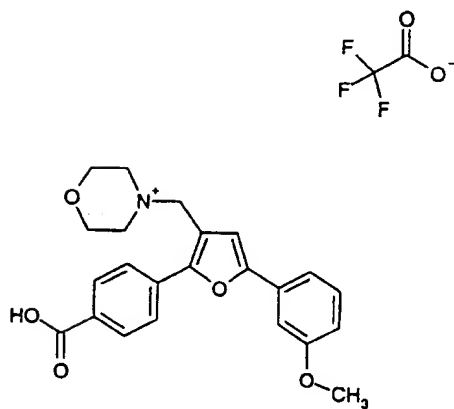


## Example 34

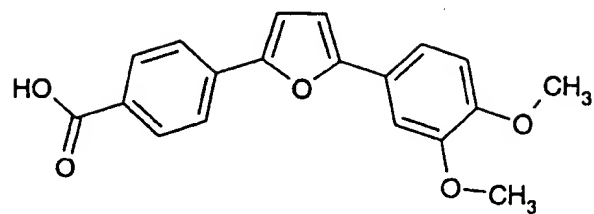


5

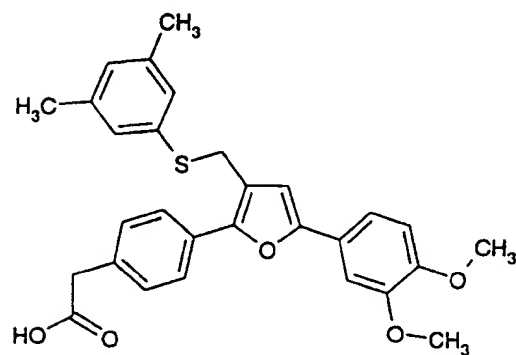
## Example 35



Example 36

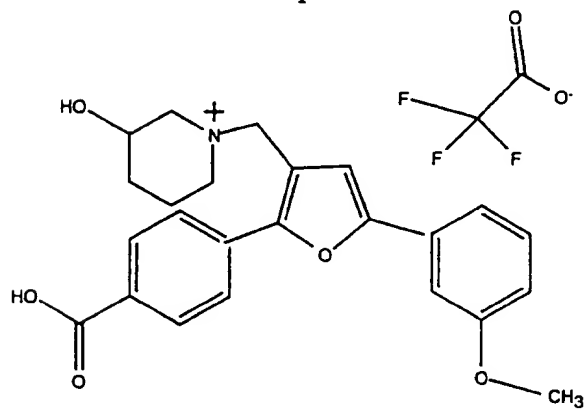


Example 37



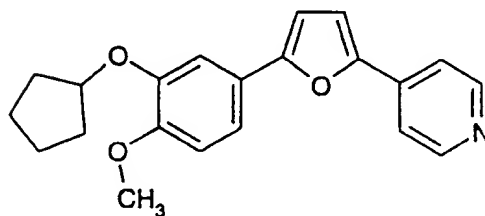
5

Example 38



10

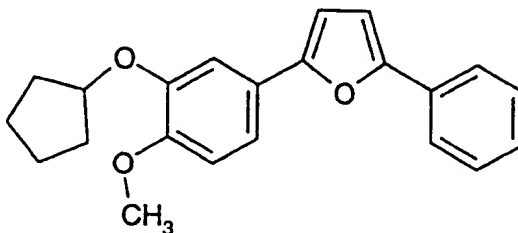
Example 39



Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.54 (d, 2H), 7.68 (d, 2H), 7.42 (dd&s, 2H), 7.25 (d, 1H), 7.05 (d, 1H), 6.9(d, 1H), 4.95 (m, 1H), 3.85 (s, 3H), 2.0-1.8 (m, 6H), 1.62 (m, 2H).

5

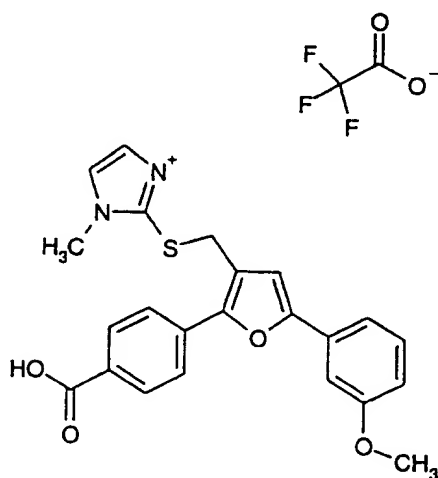
## Example 40



Proton NMR (300MHz, acetone-d<sub>6</sub>): 7.75 (s, 1H), 7.4 (t, 2H), 7.28 (m, 4H), 6.90 (d, 1H), 6.72 (d, 1H), 6.58 (d, 1H), 4.95 (m, 1H), 3.9 (s, 3H), 1.98-1.6 (m, 8H).

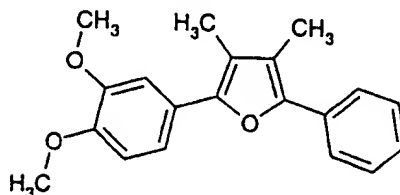
10

## Example 41



15

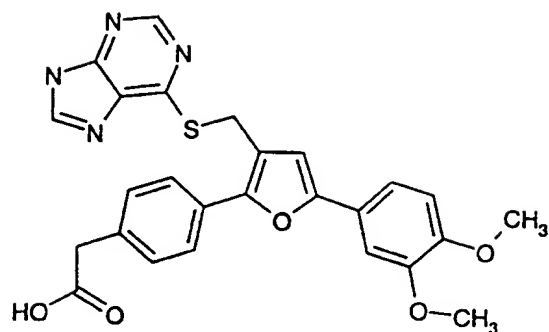
## Example 42



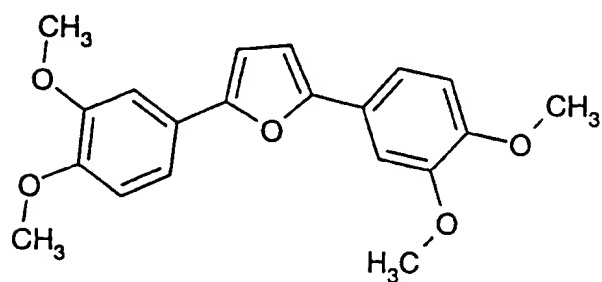
HPLC-MS 369 (M + 1)



## Example 43

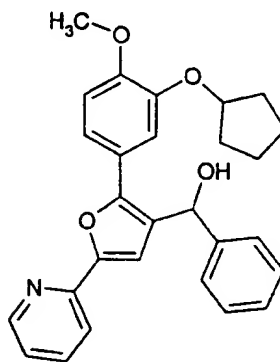


## Example 44



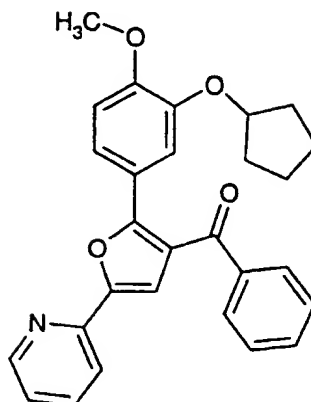
5

## Example 45



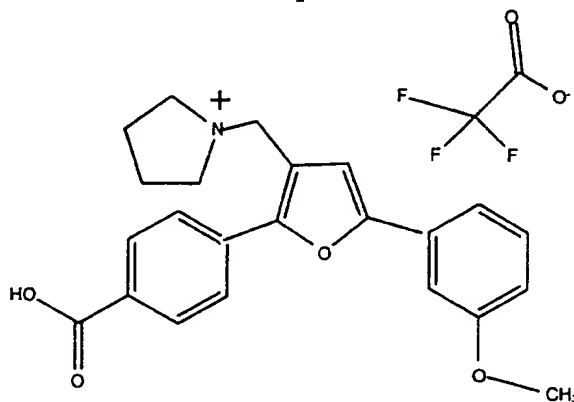
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.5(d, 1H), 7.8 (bs, 2H), 7.5 (d, 2H),  
 10 7.41 (q, 4H), 7.32 (d, 1H), 7.21 (m, 1H), 7.12 (s, 1H), 7.08 (d, 1H), 4.8 (m, 1H),  
 3.88 (s, 3H), 1.95-1.75 (m, 6H), 1.6 (m, 2H).

## Example 46



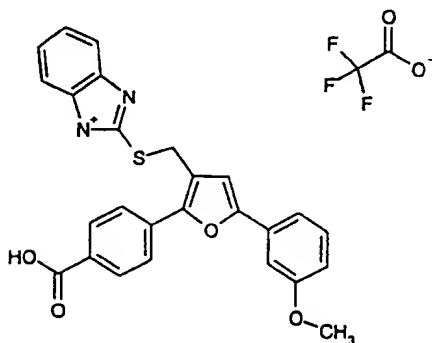
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.58(d, 2H), 7.92 (m,4H), 7.63 (d, 1H),  
 7.53 (m, 3H), 7.41 (d, 1H), 7.32 (bs, 2H), 6.98 (d, 1H), 4.63 (m, 1H), 3.82 (s,  
 5 3H), 1.85 (m, 2H), 1.75 (m, 4H) 1.53 (m, 2H).

## Example 47

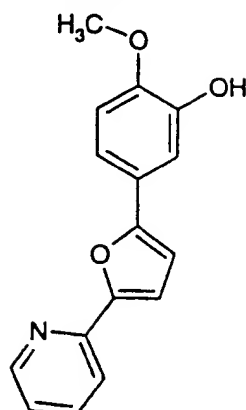


10

## Example 48

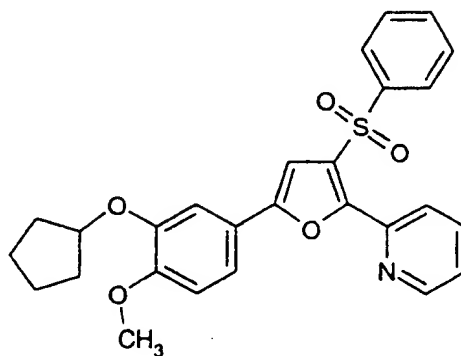


## Example 49



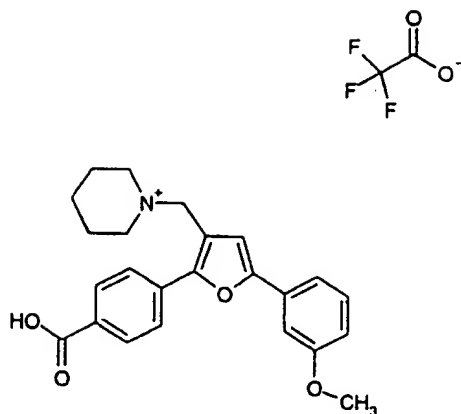
Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.55 (d, 1H), 7.85 (s, 1H), 7.80 (dd, 1H), 7.35(d, 2H), 7.22 (m, 1H), 7.15 (d, 1H), 7.04 (d, 1H), 6.82 (d, 1H), 3.88 (s, 3H).

## Example 50

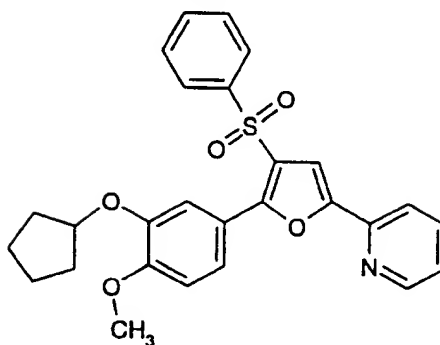


Proton NMR (300MHz, acetone-d<sub>6</sub>): 8.68 (d, 1H), 8.18 (d, 2H), 8.05 (bd, 1H), 7.92 (t, 1H), 7.62 (m, 3H), 7.45(bs, 2H), 7.35 (bs, 2H), 7.08 (d, 1H), 4.98 (m, 1H), 3.84 (s, 3H), 2.0-1.78 (m, 6H), 1.60 (m, 2H).

## Example 51



## Example 52

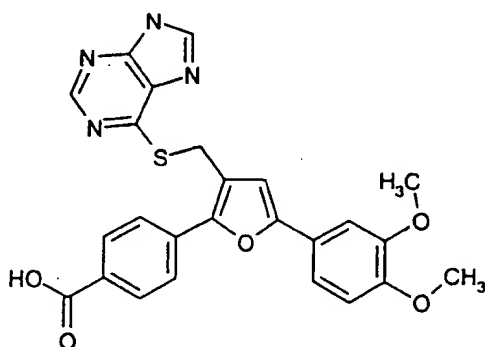


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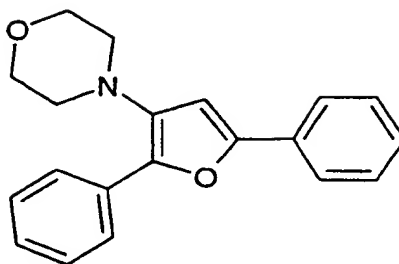
Proton NMR (300MHz, acetone- $d_6$ ): 8.61 (d, 1H), 7.91(m, 4H), 7.61(m, 5H), 7.43 (s, 1H), 7.35 (m, 1H), 7.08(d, 1H), 4.91 (m, 1H), 3.9 (s, 3H), 2.0-1.78 (m, 6H), 1.60 (m, 2H).

10

## Example 53



## Example 54



LC-MS 306 (M + 1)

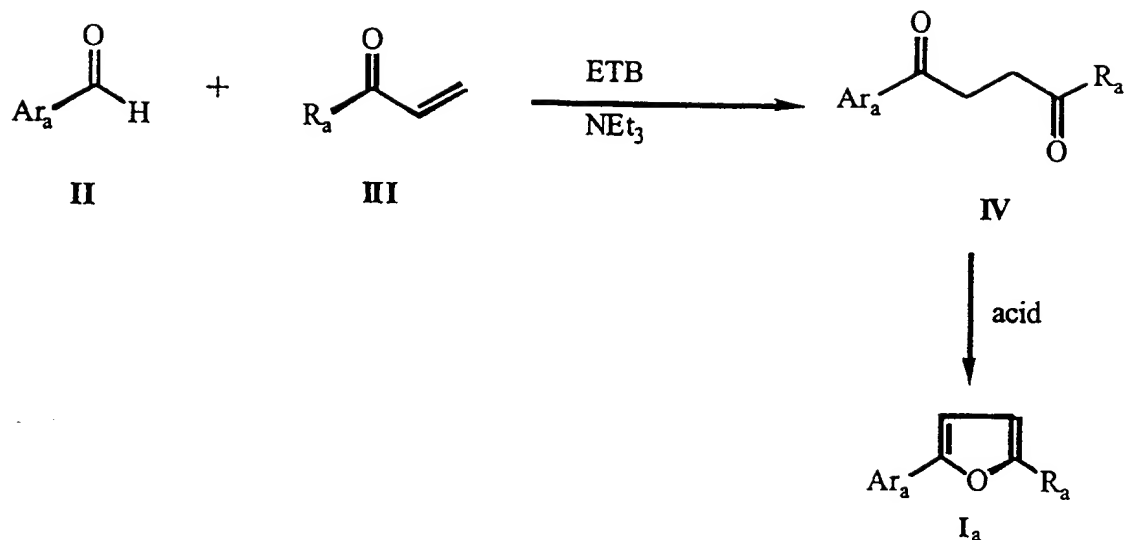
## Methods of Synthesis

5                   The compounds of the present invention can be prepared by the methods described below. It will be apparent to one skilled in the art that similar methodology could be used to prepare the enantiomers or the racemates of the illustrated compounds.

10

**METHOD A**

                  The 2,5-substituted furans of Formula I<sub>a</sub> may be prepared in a multi-step sequence from the requisite aldehyde II. Initial condensation of II with vinyl ketone III in the presence of a suitable base, such as triethylamine, and a suitable catalyst, such as ETB,  
15                   provides the diketone IV. Treatment of the diketone IV with a suitable acid such as HCl or TsOH, in an inert solvent such as toluene, MeOH or CH<sub>2</sub>Cl<sub>2</sub> converts to the 2,5-substituted furans of Formula I<sub>a</sub>.

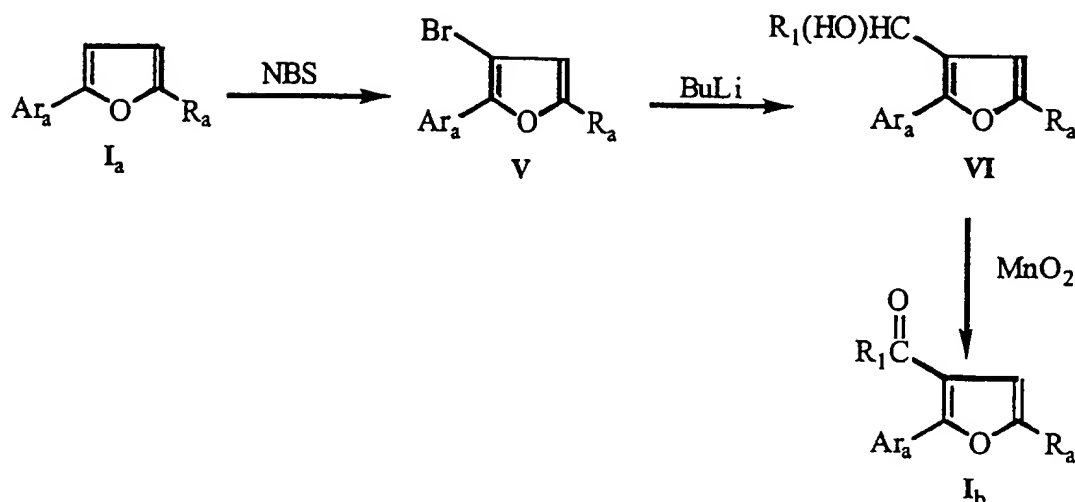


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**METHOD B**

The substituted furans of Formula I<sub>b</sub> may be prepared in a multi-step sequence from 2,5-substituted furans of Formula I<sub>a</sub>. Treatment of I<sub>a</sub> with a brominating agent such as NBS with a base such as diisopropylamine or bromine with an acid such as AcOH, provides the brominated furan V. Treatment of the furan V with a suitable base such as BuLi, in an inert solvent such as THF or ether, followed by an electrophile such as an aldehyde afforded VI. Oxidation with an agent such as MnO<sub>2</sub> gives compounds of formula 1b

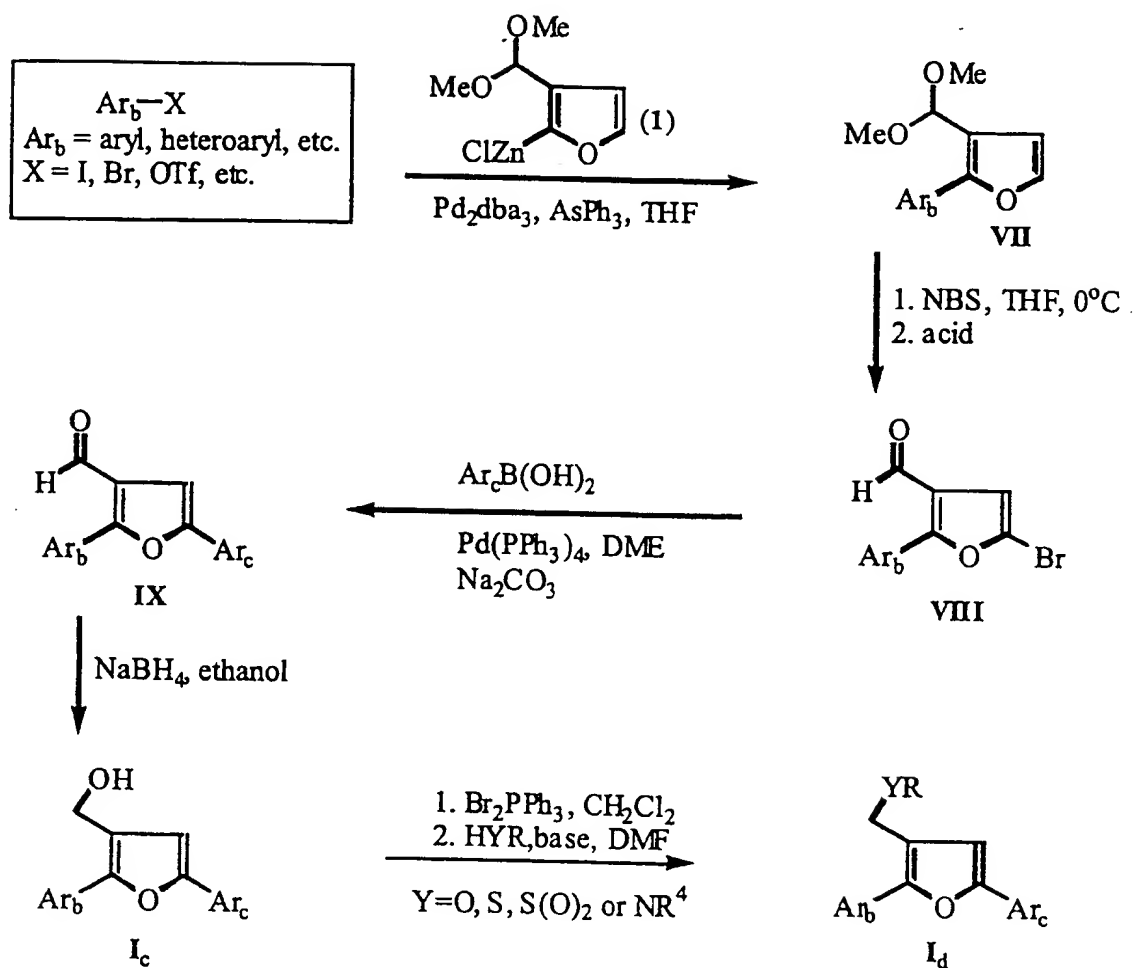
10



5

**METHOD C**

2,3,5-Tri-substituted furans of general structures **I<sub>c</sub>** and **I<sub>d</sub>** can be constructed by a multi-step scheme in solution according to scheme of method C. A suitable aryl halide (iodide or bromide) of aryl triflate was reacted with zincate 1 under the Negishi coupling reaction conditions (for a review, see: Knochel, P. *et al Chem. Rev.* (1993), 93, 2117) to yield intermediate **VII**. **VII** was then reacted with NBS in cold THF and the corresponding dimethyl acetal was hydrolyzed with a suitable acid (or with silica gel) to give aldehyde **VIII**. Subjection of **VIII** to the Suzuki cross-coupling reaction with a suitable boronic acid afforded intermediate **IX** which was reduced to the corresponding alcohol **I<sub>c</sub>**. **I<sub>c</sub>** was converted to the bromomethyl compound with dibromotriphenylphosphorane ( $\text{Br}_2\text{PPh}_3$ ) and the corresponding bromide was then reacted with nucleophiles to furnish **I<sub>d</sub>**.



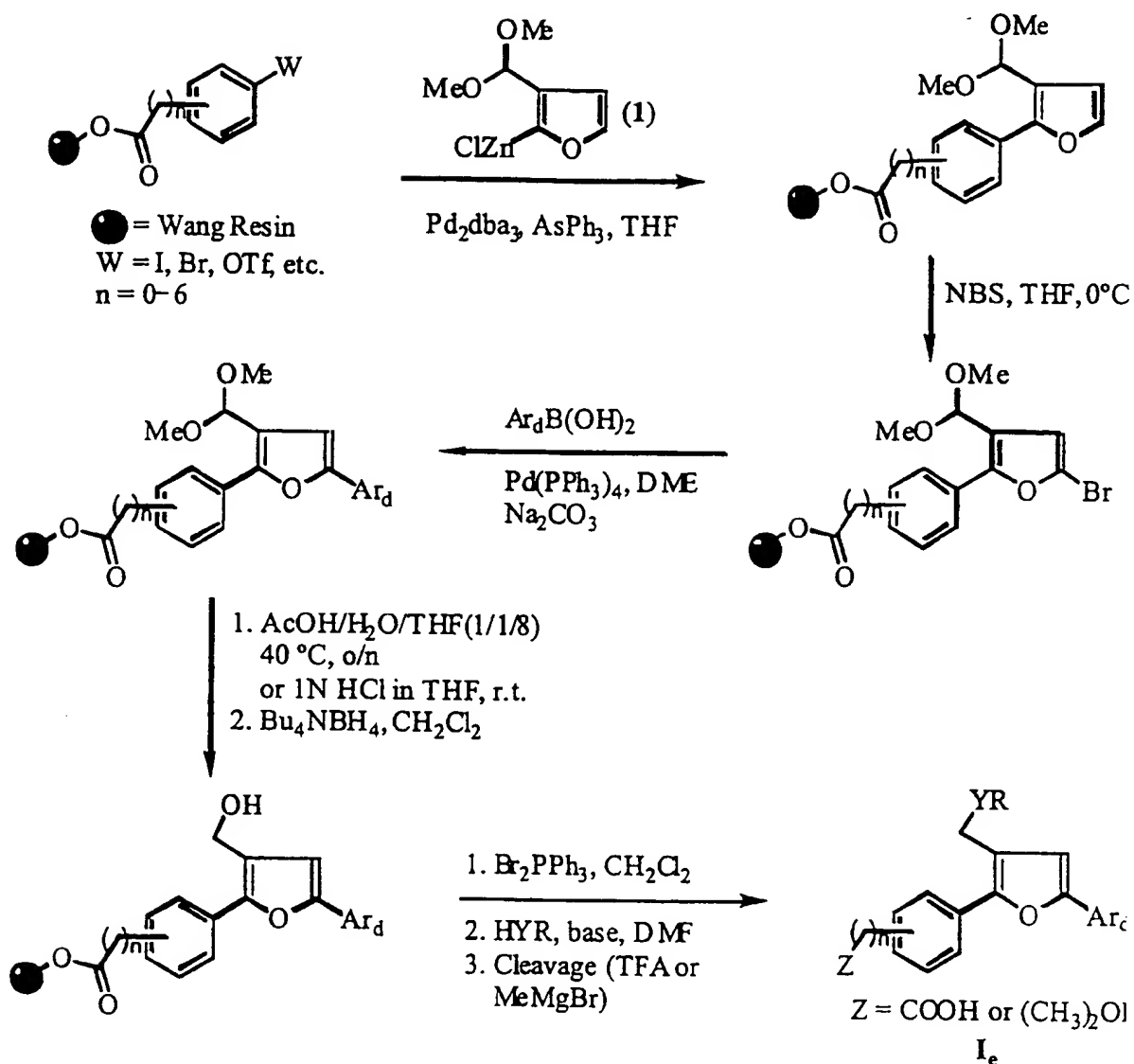
5

**METHOD D**

Compounds of general structure  $\text{I}_a$  in the invention can be constructed according to the solid phase synthetic protocol depicted below. The chemistry involved was similar to that of solution synthesis and is discussed in the experimental section

10





The invention will now be illustrated by the following non-  
 limiting examples in which, unless stated otherwise, all operations  
 were carried out at room or ambient temperature, that is, at a  
 temperature in the range 18-25°C; evaporation of solvent was carried out  
 using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-  
 30 mm. Hg) with a bath temperature of up to 60°C; the course of  
 reactions was followed by thin layer chromatography (TLC) and reaction  
 times are given for illustration only; melting points are uncorrected and

'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta ( $\delta$ ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; *etc.*: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The example numbers below correspond to the example numbers (1-54) described above. Any examples listed above that are not mentioned or described below can be made by the combination of literature described methods and/or methods disclosed herein.

The following abbreviations have the indicated meanings:

Ac	=	acetyl
Bn	=	benzyl
BSA		bovine serum albumin
cAMP		cyclic adenosine-3',5'-monophosphate
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	=	diisobutylaluminum hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
Et <sub>3</sub> N	=	triethylamine
ETB	=	3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide

GST	=	glutathione transferase
LDA	=	lithium diisopropylamide
m-CPBA	=	metachloroperbenzoic acid
MMPP	=	monoperoxyphthalic acid
MPPM	=	monoperoxyphthalic acid, magnesium salt 6H <sub>2</sub> O
Ms	=	methanesulfonyl = mesyl = SO <sub>2</sub> Me
MsO	=	methanesulfonate = mesylate
NSAID	=	non-steroidal anti-inflammatory drug
o-Tol	=	ortho-tolyl
OXONE®	=	2KHSO <sub>5</sub> •KHSO <sub>4</sub> •K <sub>2</sub> SO <sub>4</sub>
PBS		phosphate buffered saline
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PDE	=	phosphodiesterase
Pd <sub>2</sub> dba <sub>3</sub>	=	tris(dibenzylideneacetone)dipalladium(0)
Ph	=	phenyl
Phe	=	benzenediyl
PMB	=	para-methoxybenzyl
Pye	=	pyridinediyl
r.t.	=	room temperature
rac.	=	racemic
SAM	=	aminosulfonyl or sulfonamide or SO <sub>2</sub> NH <sub>2</sub>
SPA	=	scintillation proximity assay
TBAF	=	tetra-n-butylammonium fluoride
Th	=	2- or 3-thienyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic acid anhydride
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
TLC	=	thin layer chromatography
TMS-CN	=	trimethylsilyl cyanide
TNF		tumor necrosis factor
Tz	=	1H (or 2H)-tetrazol-5-yl

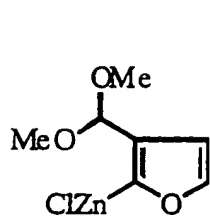
$C_3H_5$  = allyl

#### Alkyl Group Abbreviations

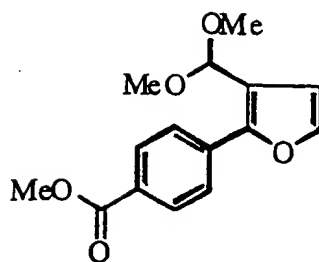
Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

- 5      The following schemes illustrate intermediates to which  
reference is made in the description of the Examples.

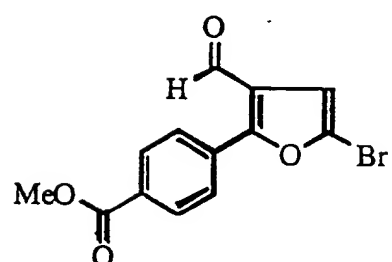
#### Intermediates and Resins



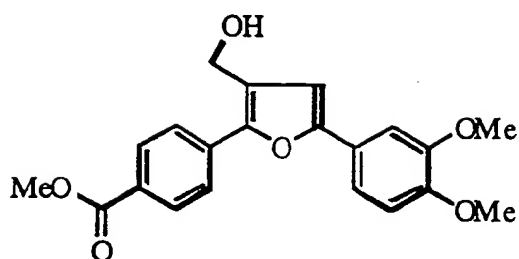
(1)



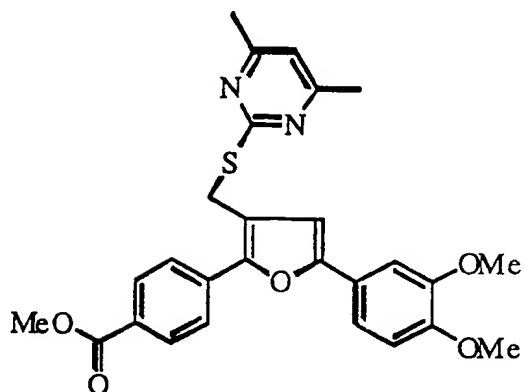
(2)



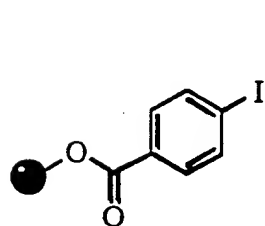
(3)



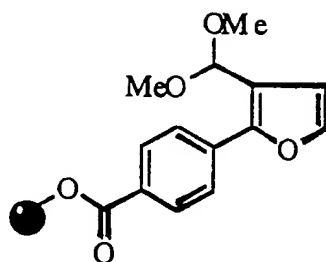
(4)



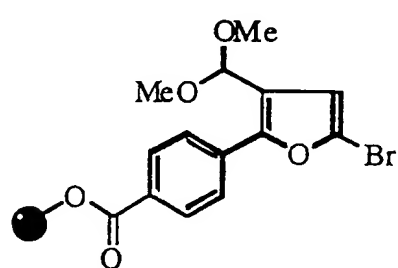
(5)



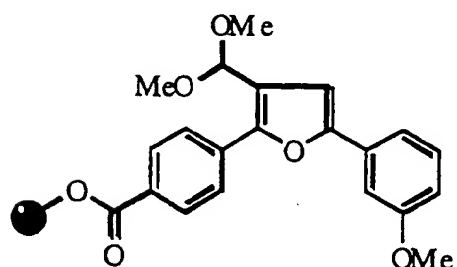
Resin A



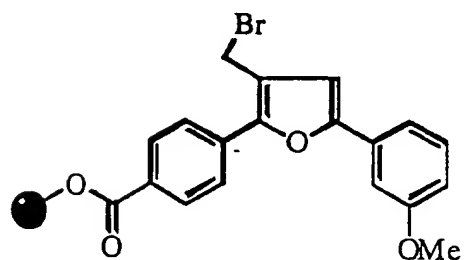
Resin B



Resin C



Resin D



Resin E

EXPERIMENTALExample 1: 2-(3-Cyclobutyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan

Step 1: 1-(3-Cyclobutyloxy-4-methoxyphenyl)-4-(2-pyridyl)-1,4 dione

- 5 A mixture of 2-pyridinecarboxaldehyde (9 g), triethyl amine (75 mL) 3-Cyclobutyloxy-4-methoxyphenyl vinyl ketone and ETB were reacted as described in *J. Med. Chem.* 1992, 35, 3474. The title compound was obtained as a white solid in 87% yield.

10 Step 2: 2-(3-Cyclobutyloxy-4-methoxyphenyl)-5-(2-pyridyl)furan

- A mixture of the dione (0.800g) from Step 1, TsOH (0.410g) in toluene (3 ml) were stirred at 105° C for 3 hours. The reaction mixture was quenched with Na<sub>2</sub>HCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried with sodium sulfate and evaporated in vacuo to afford the title compound as a beige solid in 62% yield. <sup>1</sup>H NMR (300MHz, acetone-d<sub>6</sub>): δ 1.7(m,1H), 1.85 (q, 1H), 2.18 (m, 2H), 2.51 (m, 2H), 3.85 (s, 3H), 4.80 (m, 1H), 6.85 (d, 1H), 7.05 (d,1H), 7.13 (d,1H), 7.22(m, 1H), 7.28 (d, 1H), 7.42 (dd, 2H), 7.85 (dd, 2H), 8.55 (d, 1H).

- 20 Examples 2, 3, 4, 14, 21, 39, 40, 44 and 49 were prepared accordingly.

Example 5: 2-(4-carboxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiomethyl-5-(3-methoxyphenyl)furan

Step 1. Preparation of Resin A: To a suspension of Wang resin (10.23g, 25 Novabiochem, 200-400 mesh, 1.2mmol/g) in dichloromethane (150mL) was added 4-iodobenzoyl chloride (6.4g, 24mmol), Et<sub>3</sub>N (6.7mL) and DMAP (0.5g) and the mixture was gently stirred at room temperature overnight. The suspension was filtered and the residual resin was washed sequentially with DMF, DMF/water, dichloromethane and methanol, and dried under reduced pressure to give Resin A (13.15g).

- 30 Step 2. Zincate Coupling: To a solution of 3-dimethoxymethylfuran (1.98g, 14mmol) in ether (10mL) was added n-BuLi (5.6mL, 2.5M in hexanes) at 0°C under nitrogen and the mixture was stirred at room temperature for 30 min. ZnCl<sub>2</sub> (28mL, 0.5M in THF) was introduced via a syringe and the resultant solution of Zincate 1 was added to a
- 35

suspension of Resin 1 (4.15g) in THF/ether (20mL, 2:1v/v) via a cannula at 0°C under nitrogen. To the mixture was then added a suspension of Pd<sub>2</sub>dba<sub>3</sub> (77mg)/AsPh<sub>3</sub> (103mg) in THF (3mL) and the greenish mixture was allowed to stirred at room temperature gently overnight and then  
5 filtered. The resin was washed with THF, THF/NH<sub>4</sub>Cl(30% aqueous), water, THF/water, THF, dichloromethane and methanol and then dried under reduced pressure to yield Resin B (4.2g).

Step 3. Bromination: A suspension of Resin B and NBS (1.48g) (4.15g) in THF (40mL) was stirred at 0°C for 40 min and filtered. The resin was  
10 washed with THF, DMF, THF, dichloromethane and methanol and then dried under reduced pressure to yield Resin C (4.62g).

Step 4. Suzuki Coupling: To a suspension of Resin C (2g), 3-methoxyphenyl boronic acid (793mg, 5.22mmol) in DME (8mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (100mg, 0.087mmol) and Na<sub>2</sub>CO<sub>3</sub> (2.2mL, 2M aqueous)  
15 and the mixture was deoxygenated under a stream of nitrogen for 5 min and then heated to reflux for 6h. After cooling to room temperature, the mixture was filtered and the residual resin was washed with DMF, DMF/water, water, DMF/water, DMF, dichloromethane and methanol and then dried under reduced pressure to afford Resin D.

Step 5. Preparation of Resin E: A suspension of Resin D (2g) in H<sub>2</sub>O/AcOH/THF (20mL, 1:1:8) was shaken on an orbital shaker vigorously at 40°C overnight and filtered. The resin was washed with THF, dichloromethane and methanol and dried under reduced  
20 pressure. The dried resin was then suspended in dichloromethane (29mL) and Bu<sub>4</sub>NBH<sub>4</sub> (885mg) was added and the mixture was again shaken at room temperature overnight and filtered. The residual resin was washed with dichloromethane, DMF, THF and methanol and dried under reduced pressure. To the resin (1.45g) suspended in  
25 dichloromethane (30mL) was added Br<sub>2</sub>PPh<sub>3</sub> (1g) and the mixture was stirred at room temperature for 1h and filtered. The resin was then washed with dichloromethane, DMF, THF, ethyl acetate and ether and then dried under reduced pressure to yield Resin E.

Step 7. Cleavage with TFA: 200 mg of Resin E was reacted with 5 eq of 4,6-dimethyl-2-mercaptopyrimidine in DMF (2mL) in the presence of 6 eq  
35 of diisopropyl-ethylamine for 1h and worked up as usual. 80mg of the

dried resin was then cleaved with 20%TFA in dichloromethane (containing 5% dimethyl sulfide) for 20 min and filtered. The resin was washed with dichloromethane (3 x) and the filtrate and washing solutions were combined, concentrated and lyophilized to give the title compound as a yellow solid. <sup>1</sup>H NMR: see Table 1. Cleavage of the same resin with MeMgBr (14 eq) in THF afforded example 6. Examples 8, 10, 12, 13, 17, 18, 19, 20, 24, 25, 26, 27, 29, 30, 34, 35, 36, 38, 41, 47, 48, 51 and 53 were prepared accordingly.

10 Example 6: 2-(4-(1-Hydroxy-1-methylethyl)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiomethyl-5-(3-methoxyphenyl)furan

200 mg of resin E was reacted as described in step 7 of example 5. Cleavage of the resin with MeMgBr (14 eq) in THF afforded the title compound.

15 Example 7: 3-Acetoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl)furan

A mixture of 2-(3-Cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan, (50 mg) from example 2, in acetic acid (2ml) and bromine were stirred for 15 mins. at room temperature. The reaction mixture was quenched with sodium sulfite, extracted with EtOAc, dried with sodium sulfate and evaporated in vacuo to afford the unexpected title compound as a beige solid in 31% yield. <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.6 (m, 2H), 1.98-1.8 (m, 6H), 2.3 (s, 3H), 3.88 (s, 3H), 4.82 (m, 1H), 6.91 (dd, 1H), 7.10 (m, 1H), 7.25 (s, 1H), 7.35 (dd, 2H), 7.7 (bs, 2H), 8.58 (d, 1H).

Example 11: 2-(4-Carboxyphenyl)-5-(3,4-dimethoxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiomethylfuran

30 Step 1. Preparation of Zincate 1: To a solution of 3-dimethoxymethylfuran (see: Koenig, H. *et al*, (1981) *Liebigs Ann. Chem.* 668) (845mg, 5.95mmol) in diethyl ether (10mL) at -78°C under nitrogen was added n-BuLi (2.4mL, 2.5M in hexanes) and the mixture was allowed to warm up to room temperature and then heated to reflux for 10 min. ZnCl<sub>2</sub> (12mL,



0.5M in THF) was then introduced *via* a syringe after the mixture was cooled to room temperature to yield zincate 1.

- Step 2. Preparation of Intermediate 2: To the zincate solution under
- 5 nitrogen at room temperature was added methyl 4-iodobenzoate (770mg, 2.97mmol) and a suspension of  $\text{Pd}_2\text{dba}_3/\text{AsPh}_3$  in THF (2mL). The mixture was then stirred at room temperature for 20 min and then quenched with  $\text{NH}_4\text{Cl}$  (saturated aq) and extracted with ether. The extract was washed with water, brine, dried over  $\text{MgSO}_4$  and filtered.
- 10 The filtrate was concentrated and purified by flash chromatography (5% ethyl acetate in hexanes + 1%  $\text{Et}_3\text{N}$ ) to yield 2 (750mg, 92%).  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$ 8.07 (d, 2H), 7.86 (d, 2H), 7.67 (d, 1H), 6.71 (d, 1H), 5.62 (s, 1H), 3.89 (s, 3H), 3.33 (s, 6H).
- Step 3. Preparation of Intermediate 3: A mixture of compound 2 (630mg, 2.28mmol) and NBS (643mg) in THF (10mL) was stirred at 0°C for 30 min and quenched with 5% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , and the mixture was worked up as usual. The crude product thus obtained was subjected to flash chromatography (20% ethyl acetate in hexanes) to yield compound 3
- 15 (531mg, 75%) as a white solid after recrystallization from ether/hexanes.  $^1\text{H}$  NMR (400MHz, acetone- $d_6$ ):  $\delta$ 10.13 (s, 1H), 8.17 (d, 2H), 8.03 (d, 2H), 7.00 (s, 1H), 3.93 (s, 3H).

- Step 4. Preparation of Intermediate 4: To a solution of compound 3
- 25 (150mg, 0.485mmol) in DME (3mL) was added 3,4-dimethoxyphenyl boronic acid (97mg, 0.53mmol),  $\text{Pd}(\text{PPh}_3)_4$  (17mg) and  $\text{Na}_2\text{CO}_3$  (0.27mL, 2M aq) and the mixture was deoxygenated under a stream of nitrogen for 5 min and heated to reflux for 3h. The mixture was then cooled to room temperature, diluted with water, extracted with ethyl acetate (3 x
- 30 5mL). The extracts were combined, washed with water, brine, dried over  $\text{MgSO}_4$  and filtered. The filtrate was concentrated in *vacuo* and the residue dissolved in a 1:1 mixture of THF/ethanol. To the solution was added excess  $\text{NaBH}_4$  and the mixture stirred at room temperature for 10 min, quenched with  $\text{NH}_4\text{Cl}$  (aq) and extracted with ethyl acetate (3 x
- 35 10mL). The extracts were then washed with brine, dried (over  $\text{MgSO}_4$ )

and concentrated. The crude product was then purified by flash chromatography (40% ethyl acetate in  $\text{CH}_2\text{Cl}_2$ ) to furnish intermediate 4 (170mg, 95% yield) as a bright yellow fluorescent solid.  $^1\text{H}$  NMR (300MHz, acetone- $\text{d}_6$ ):  $\delta$  8.08 (d, 2H), 7.90 (d, 2H), 7.40 (m, 2H), 7.03 (d, 1H), 6.96 (s, 1H), 4.75 (d, 2H), 4.36 (t, 1H, OH), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H).

Step 5. Intermediate 5: To a solution of 4 (170mg, 0.46mmol) in dichloromethane (5mL) was added  $\text{Br}_2\text{PPh}_3$  (234mg, 0.55mmol) and the mixture was stirred at room temperature for 30 min. To the mixture was added 4,6-dimethyl-2-mercaptopyrimidine (129mg) and diisopropylethylamine (0.24mL) and the solution stirred at room temperature for 1h, concentrated and the residue was purified by flash chromatography (60% ethyl acetate in hexanes) to afford 5 (190mg, 84%) as a bright yellow fluorescent solid.  $^1\text{H}$  NMR (300MHz, acetone- $\text{d}_6/\text{CDCl}_3$ ):  $\delta$  8.08 (d, 2H), 7.95 (d, 2H), 7.37-7.35 (m, 2H), 7.00 (d, 1H), 6.96 (s, 1H), 6.87 (s, 1H), 4.55 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 2.32 (s, 6H).

Step 6. Hydrolysis: A mixture of compound 5 (16mg, 0.032mmol), LiOH (0.4mL, 1M solution in water) in dioxane (0.7mL) was heated to  $60^\circ\text{C}$  for 5h and cooled to room temperature. The mixture was then acidified with acetic acid and extracted with ethyl acetate. The extract was washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated to give the title compound as a bright yellow solid.  $^1\text{H}$  NMR: see Table 1.

Example 28: 5-(3,4-Dimethoxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiomethyl-2-[4-(1-hydroxy-1-methylethyl)phenyl]furan

To a solution of compound 5 from Example 11 (160mg, 0.33mmol) in THF (3mL) under nitrogen was added  $\text{MeMgBr}$  (1.2mL, 1.4M in THF/toluene) and the mixture was stirred at room temperature for 30 min, quenched with  $\text{NH}_4\text{Cl}$  and extracted with ethyl acetate. The crude product was purified by flash chromatography (70% ethyl acetate in hexanes) to the title compound as a bright yellow solid (149mg, 93%).  $^1\text{H}$  NMR: see Table 1.

Example 31: 3-Bromo-2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan

A mixture of 2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan, (0.5 g) example 2, in  $\text{CH}_2\text{Cl}_2$  (3ml) and diisopropylamine (21ul) and NBS (0.320g) were stirred for 20 mins. at room temperature. The reaction mixture was quenched with  $\text{Na}_2\text{CO}_3$  extracted with  $\text{CH}_2\text{Cl}_2$  dried with sodium sulfate and evaporated in vacuo to afford the title compound as a beige solid in 63% yield.  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  1.6 (m, 2H), 2.0-1.8 (m, 6H), 3.90 (s, 3H), 4.95 (m, 1H), 7.05 (dd, 1H), 7.23 (m, 2H), 7.43 (m, 2H), 7.85 (dd, 2H), 8.5 (dd, 1H).

Example 45: 3-Alphaphenylmethanol-2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl)furan

To a mixture 3-bromo-2-(3-Cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan (from Example 31) in THF (2ml) at -78C was added nBuLi 1.5M (.2ml) . After 5 mins. benzaldehyde (20ul) was added The reaction mixture was quenched with  $\text{NH}_4\text{Cl}$  extracted with EtOAc dried with sodium sulfate and evaporated in vacuo to afford the title compound as a beige solid in 42% yield.  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  1.6 (m, 2H), 1.95-1.8 (m, 6H), 3.88 (s, 3H), 4.8 (m, 1H), 6.0 (s, 1H), 7.12 (s, 1H), 7.08(d, 1H), 7.21 (m, 1H), 7.32 (d, 1H), 7.41 (q, 4H), 7.5 (d, 2H), 7.8 (bs, 2H), 8.5 (d, 1H). Examples 22, 50 and 52 were prepared accordingly.

Example 46: 3-Benzoyl-2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl)furan

A mixture 3-alphaphenylmethanol-2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(2-pyridyl) furan (24 mg, Example 45) in EtOAc (1ml) and manganese dioxide were stirred for 2 hrs. The reaction mixture was filtered through celite . Flash chromatography (20% EtOAc in hexanes) afford the title compound as a beige solid in 90% yield.  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  1.53 (m, 2H), 1.75 (m, 4H), 1.85 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 6.98 (d, 1H), 7.32(bs, 1H), 7.32 (bs, 2H), 7.41(d, 1H), 7.53 (m, 3H), 7.63(d, 2H), 7.92 (m, 4H), 8.58 (d, 2H). Examples 9 and 16 were prepared accordingly.

## ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

Establishment of CHO-K1 cell lines stably expressing PDE IVa enzyme

5 CHO-K1 cells stably expressing the prostacyclin receptor and grown under G418 selection as described previously (Y. Boie, *et al*, J. Biol. Chem.: 269, 12173-12178, 1994) were plated at a density of  $1.75 \times 10^6$  cells/175cm<sup>2</sup> in a T-175 flask (Gibco, Burlington, VT) containing alpha MEM media; 10% heat inactivated fetal bovine serum (FBS); 1% (v/v) penicillin/streptomycin; 25 mM Hepes, pH 7.4; and 500 µg/ml G418  
10 (complete media). The cells were placed in an incubator for 24 hr at 37°C and 5% CO<sub>2</sub>. The cells were then washed with warmed sterile phosphate buffered saline (PBS) and incubated with 2µg/ml DNA, and 9 µg/ml lipofectamine reagent in Opti-MEM for 7 hr. At 37°C and 5% CO<sub>2</sub>. The incubation solution was diluted 1:2 with Opti-MEM containing 20%  
15 FBS and incubated overnight. Following the overnight incubation, the media was replaced by complete media containing 500 µg/ml hygromycin B. Colonies were identified and grown in T-175 flasks for further characterization.

20 Measurement of whole-cell cAMP content

CHO-K1 cells were plated at a density of  $10^6$  cells/175 cm<sup>2</sup> containing complete media with 500 µg/ml hygromycin. The flasks were maintained in an incubator at 37°C with 5.0% CO<sub>2</sub> for 72 hr. The media was changed and the cells were allowed to grow overnight. The cells  
25 were washed and dissociated from the plate with PBS containing 0.5 mM EDTA. Cellular cAMP content was measured by centrifuging the cell suspension at 150 g x 10 min. And resuspending the cells in a Hanks buffered salt solution at a density of  $0.2 \times 10^6$  cells/ml. The cells were preincubated at room temperature for 15 min. and then incubated with  
30 10 µM prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) and the indicated compound for an additional 10 min. Basal cAMP levels were determined by incubating the cells in 0.1% DMSO. The incubations were terminated by the addition of HCl (0.1 N final) and the cells measured for cAMP as described below.

Determinations of whole-cell cAMP content were performed by incubating 100  $\mu$ l reconstituted rabbit anti-succinyl cAMP serum with 100  $\mu$ l of the whole-cell reaction or known cAMP standard and 30 pmol of  $^{125}$ I-cAMP TME in a ScintiStrip<sup>TM</sup> well (300  $\mu$ l final volume) at room temperature for 18 h. Total cpm ( $B_0$ ) was determined in the absence of sample of cAMP standard. The reaction mixture was then aspirated out of the well, and the individual wells were counted in a Beckman LS 6000SC with the window open from 10-999 for 1 min. The data were expressed as  $\%B/B_0 = [(standard\ or\ sample\ cpm - non-specific\ cpm) / (B_0\ cpm - non-specific\ cpm)] \times 100$ . Non-specific cpm were determined by incubating only the  $^{125}$ I-cAMP TME with assay buffer (50 nM acetate; pH 5.8) in the ScintiStrip<sup>TM</sup> well. All determinations were performed in triplicate.

#### 15 The Elevation of cAMP in Leukocytes

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intraperitoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The most potent compounds according to the Examples induced a concentration-dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1 $\mu$ M.

#### Human Whole Blood Assay

Fresh blood was collected in heparinized tubes by venipuncture from healthy volunteers. These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 7

days prior to blood collection. Five hundred  $\mu\text{L}$  aliquots of human blood were initially pre-incubated with either 2  $\mu\text{L}$  DMSO (vehicle) or 2  $\mu\text{L}$  of a test compound at a final concentration of up to 100  $\mu\text{M}$ . Fifteen min later, the blood was incubated with lipopolysaccharide (LPS) at 1  $\mu\text{g}/\text{ml}$  (Sigma Chem, #L-2630 from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA/PBS) for 24 h at 37°C. At the end of the 24 h incubation, the blood was further incubated with an additional amount of LPS (final concentration: 1  $\mu\text{g}/\text{ml}$ ) for 30 min. This was followed by incubation with f-Met-Leu-Phe (f-MLP) at 1  $\mu\text{M}$  for 15 min. The blood was then centrifuged at 3,300 rpms for 10 min to obtain plasma. The plasma was de-proteinized with methanol and the supernatant was assayed for TNF- $\alpha$  using a commercial ELISA kit (Cistron) and for LTB<sub>4</sub> using a EIA kit developed at Merck Frosst. The instant compounds showed IC<sub>50</sub> values ranging from 1 nM to 5  $\mu\text{M}$ .

#### Human Mononuclear Cell Assay

Fresh blood was collected from healthy male volunteers by venipuncture into tubes containing sodium citrate as anticoagulant (10%). The blood was layered on top of histopaque and was centrifuged at 1400 rpm for 35 min at room temperature. After centrifugation, a distinct layer of mononuclear cells (monocytes and lymphocytes) located between the blood and histopaque layers could be aspirated off using a transfer pipette. The mononuclear cells were resuspended in calcium and magnesium free PBS and diluted to  $2 \times 10^6$  cells/ml. One hundred  $\mu\text{L}$  aliquots of mononuclear cells were mixed with 2  $\mu\text{L}$  of DMSO (vehicle) or a test compound at a final concentration of up to 10  $\mu\text{M}$  in the presence of 1% or 25% heat-inactivated human serum. Fifteen min. later, the cells were incubated with LPS at a final concentration of 1  $\mu\text{g}/\text{ml}$  at 37°C for 20 h. At the end of the incubation period, the supernatant was obtained by centrifugation at 1000 rpm for 10 min and was assayed for TNF- $\alpha$  using a commercial ELISA kit (Cistron). The instant compounds showed IC<sub>50</sub> values ranging from 0.1 nM to 5  $\mu\text{M}$ .

#### In Vivo inhibition of allergen induced bronchoconstriction

Guinea pigs, 200 g, are sensitized with a 100µg/ml ovalbumin in an Al<sub>2</sub>O<sub>3</sub> suspension in physiological saline. Five hundred µl of this solution are injected intraperitoneally and another 500 µl are injected in 6 ganglionic regions (±75 µl/site). The animals are then  
5 housed for 4 to 6 weeks. Thirty minutes prior to the experimentation, the guinea pigs are treated with the test compound or vehicle and with mepyramine maleate, 1 mg/kg. The injection volume is 1 ml/kg of body weight.

After pre-treatment, the animals are placed in a whole body  
10 plethysmograph for conscious unrestrained guinea pigs. The animals are challenged for one minute with an aerosol containing ovalbumin in a concentration of 1% in physiological saline. The changes in pulmonary function assessed as changes in enhanced pause or Penh. Penh, a marker of bronchoconstriction, is defined as follows:

15  $Penh = [(expiratory\ time / relaxation\ time) - 1] * [(peak\ expiratory\ flow / peak\ inspiratory\ flow)]$

The results are expressed as the percentage of inhibition of the Penh increase versus the response obtained in a control experiment.

20 SPA based PDE activity assay protocol for measuring inhibition of phosphodiesterase activity

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in 96-well plate format as follows:

25 In a 96 well-plate at 30 °C was added the test compound (dissolved in 2 µl DMSO), 188 µl of substrate buffer containing [2,8-<sup>3</sup>H] adenosine 3',5'-cyclic phosphate (cAMP, 100 nM), 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 50 mM Tris, pH 7.5. The reaction was initiated by the addition of 10 µl of human recombinant PDE-IV isozymes, either expressed and  
30 purified from sf9 cells, or from CHO-K1 cells (the amount was controlled so that ~ 10% product was formed in 10 min. at 30 °C). The reaction was stopped after 10 min. by the addition of 1 mg of PDE-SPA beads (Amersham). The product AMP generated was quantified on a Microbeta 96-well plate counter. The signal in the absence of enzyme

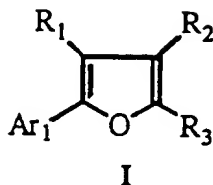
was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. The IC<sub>50</sub> value was approximated by the non-linear regression fitting of a  
5 ten point titration using the standard 4 parameter equation.

IC<sub>50</sub> values were determined with 100 nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. The instant compounds were shown to have IC<sub>50</sub>  
10 values of 10nM to 3μM.



## WHAT IS CLAIMED IS:

## 1. A compound of Formula I



5

or a pharmaceutically acceptable salt thereof wherein:

Ar<sup>1</sup> is an aromatic ring selected from phenyl, pyridinyl, or furyl,  
 10 optionally substituted with up to two substituents chosen independently  
 from among:

- a) C<sub>1</sub>-6alkyl, optionally substituted with -OH, -CO<sub>2</sub>H, CO<sub>2</sub>C<sub>1</sub>-3alkyl, and CN,
- b) C<sub>1</sub>-6alkoxy,
- 15 c) C<sub>1</sub>-3alkylthio,
- d) C<sub>1</sub>-3alkylsulfonyl,
- e) C<sub>1</sub>-3fluoroalkyl, optionally substituted with -OH,
- f) halo,
- g) -OH,
- 20 h) -CO<sub>2</sub>H,
- i) -CO<sub>2</sub>C<sub>1</sub>-3alkyl,

R<sup>1</sup> is selected from:

- a) hydrogen, b) halo, c) C<sub>1</sub>-C<sub>5</sub>alkylcarbonyloxy,
- 25 d) C<sub>1,3</sub>alkyl, optionally substituted with -OH, N-C<sub>1,4</sub>alkyl, cyclo-
- N-C<sub>5,7</sub>alkyl, piperazine, C<sub>1,4</sub>alkylcarbonylpiperazine, morpholine or hydroxypiperidine,
- e) C<sub>1,4</sub>alkylcarbonyl,
- 30 f) tri(C<sub>1,3</sub>alkyl)silyl,
- g) N-morpholinyl,
- h) -X-Y-Ar<sup>2</sup>,

wherein:

5 X is 1) -CH<sub>2</sub>-,  
2) -CO-, or  
3) a bond;

Y is 1) -O-,  
2) -S-,  
3) -S(O)<sub>2</sub>-,  
4) -NR<sup>4</sup>-, or  
10 5) a bond;

Ar<sup>2</sup> is an aromatic ring selected from phenyl,  
benzothiazolyl, benzoxazolyl, pyrimidinyl, pyridinyl, purinyl or  
imidazolyl optionally substituted with up to two substituents chosen  
independently among:

15 1) C<sub>1-6</sub>alkyl,  
2) C<sub>1-6</sub>alkoxy,  
3) -OH,  
4) halo, or  
5) CF<sub>3</sub>;

20

R<sup>2</sup> is selected from:

a) hydrogen or  
b) C<sub>1-3</sub>alkyl.

R<sup>3</sup> is selected from phenyl, pyridinyl, quinolinyl or furyl, optionally  
25 substituted with up to two substituents chosen independently among:

a) C<sub>1-3</sub>alkyl,  
b) C<sub>1-3</sub>fluoroalkyl,  
c) C<sub>1-6</sub>alkoxy,  
d) C<sub>1-3</sub>fluoroalkoxy,  
30 e) C<sub>1-3</sub>alkylthio,  
f) halo,  
g) -OH,

R<sup>4</sup> is chosen from among:

a) hydrogen, or  
35 b) C<sub>1-5</sub>alkyl.

2. A compound according to Claim 1 wherein:

R<sup>2</sup> is hydrogen;

5 and the remaining substituents are defined as in Claim 1.

3. A compound according to Claim 1 wherein:

-X-Y- is -CH<sub>2</sub>-S-,

and the remaining substituents are defined as in Claim 1.

10

4. A compound according to Claim 1 wherein:

Ar<sup>2</sup> is pyrimidinyl, optionally substituted with up to two substituents  
chosen independently among:

- 15
- 1) C<sub>1</sub>-6alkyl,
  - 2) C<sub>1</sub>-6alkoxy,
  - 3) -OH, or
  - 4) halo,

and the remaining substituents are defined as in Claim 1.

20

5. A compound according to Claim 1 wherein

Ar<sup>1</sup> is an aromatic ring selected from phenyl, pyridinyl or furyl,  
optionally substituted with up to two substituents selected independently  
from among:

- 25
- a) C<sub>1</sub>-6alkyl, optionally substituted with -OH, -CO<sub>2</sub>H, CO<sub>2</sub>C<sub>1</sub>-  
3alkyl, and CN,
  - b) C<sub>1</sub>-6alkoxy,
  - c) C<sub>1</sub>-3alkylthio,
  - d) C<sub>1</sub>-3alkylsulfonyl,
  - e) C<sub>1</sub>-3fluoroalkyl, optionally substituted with -OH,
  - 30 f) halo,
  - g) -OH,
  - h) -CO<sub>2</sub>H,
  - i) -CO<sub>2</sub>C<sub>1</sub>-3alkyl,

35 R<sup>1</sup> is selected from:

- a) hydrogen,
- b) halo,
- c) C<sub>1-3</sub> alkyl, optionally substituted with OH,
- h) -X-Y-Ar<sup>2</sup>,

5    wherein:

- X is
- 1) -CH<sub>2</sub>-,
  - 2) -CO-, or
  - 3) a bond;
- Y is
- 1) -O-,
  - 10    2) -S-,
  - 3) -S(O)<sub>2</sub>-,
  - 4) -NR<sup>4</sup>-, or
  - 5) a bond;

15    Ar<sup>2</sup> is an aromatic ring selected from phenyl, pyrimidinyl, pyridinyl, purinyl or imidazolyl optionally substituted with up to two substituents selected independently among:

- 1) C<sub>1-6</sub>alkyl,
- 2) C<sub>1-6</sub>alkoxy,
- 3) -OH,
- 20    4) halo, or

R<sup>2</sup> is selected from:

- a) hydrogen or
- b) C<sub>1-3</sub>alkyl.

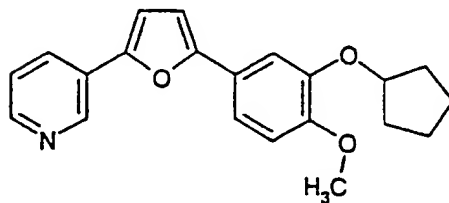
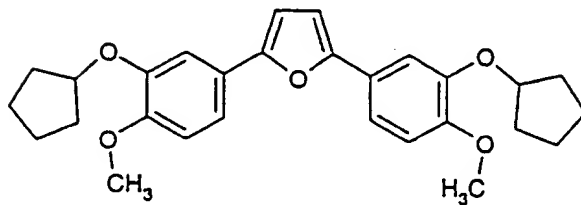
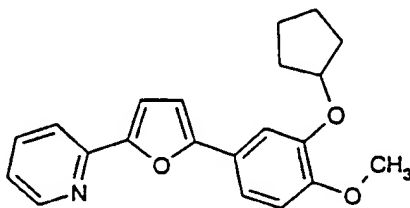
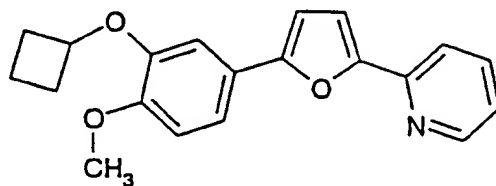
25    R<sup>3</sup> is selected from phenyl, pyridinyl, or quinolinyl, optionally substituted with up to two substituents chosen independently among:

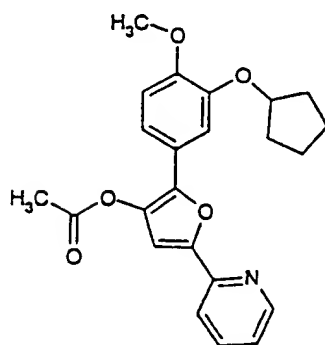
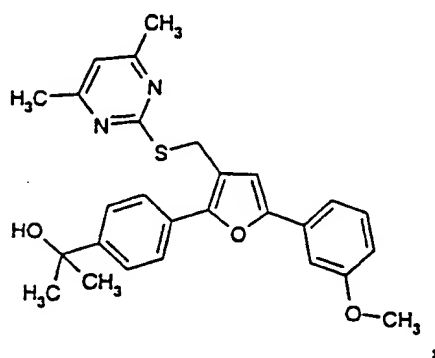
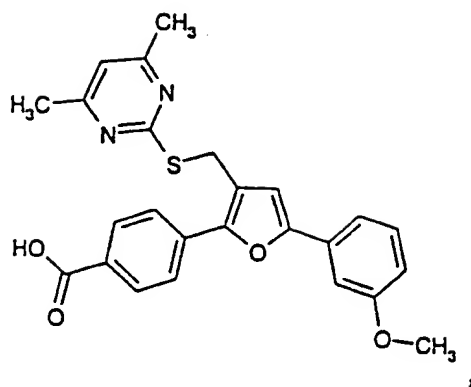
- a) C<sub>1-3</sub>alkyl,
- b) C<sub>1-3</sub>fluoroalkyl,
- c) C<sub>1-6</sub>alkoxy,
- 30    d) C<sub>1-3</sub>fluoroalkoxy,
- e) C<sub>1-3</sub>alkylthio,
- f) halo, or
- g) -OH, and

35    R<sup>4</sup> is chosen from among:

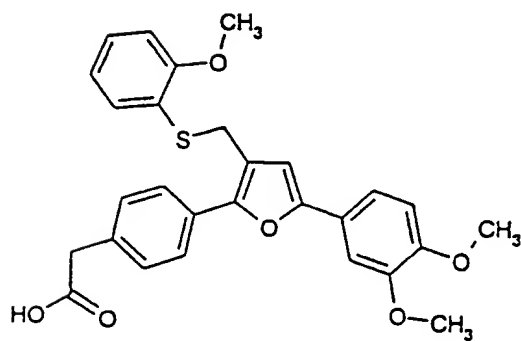
- a) hydrogen, or  
b) C<sub>1-5</sub>alkyl.

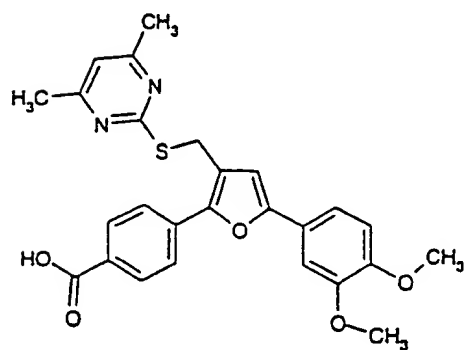
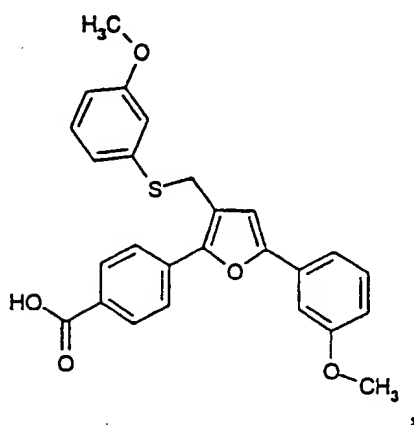
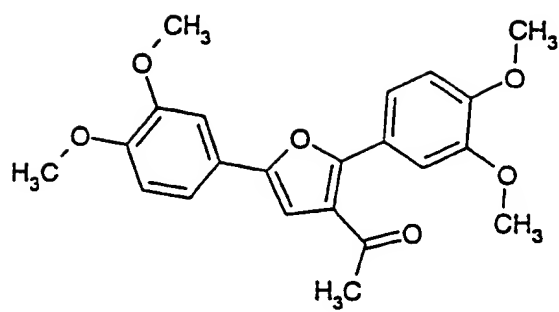
6. A compound according to Claim 1 selected from the  
5 group consisting of

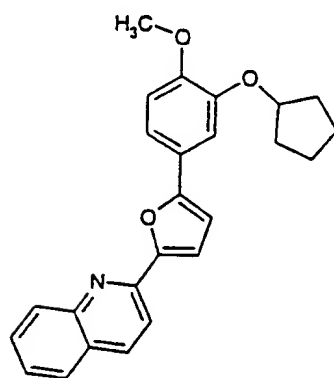
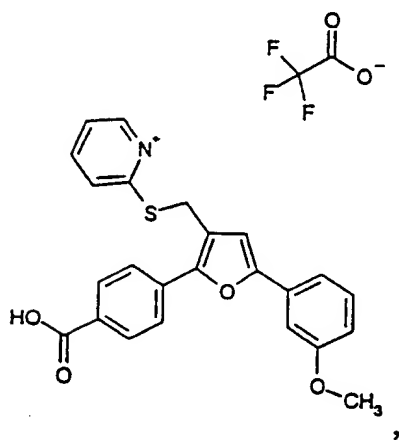
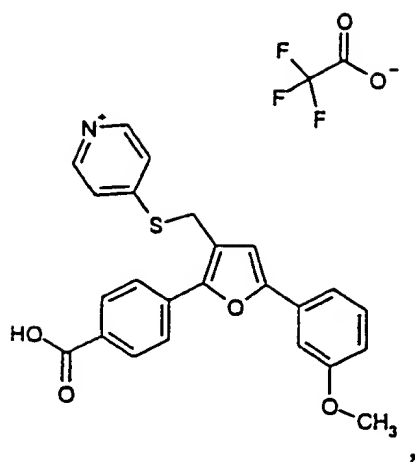




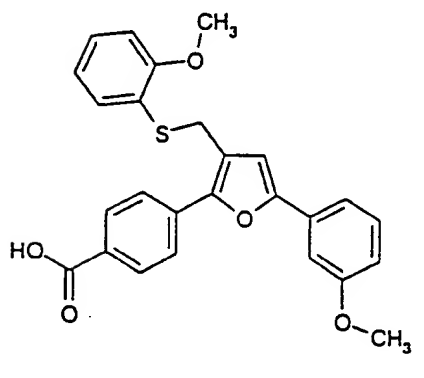
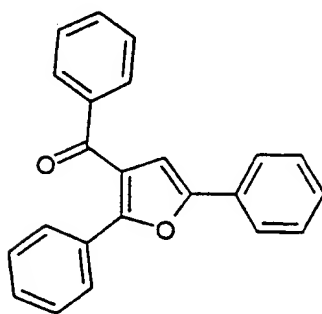
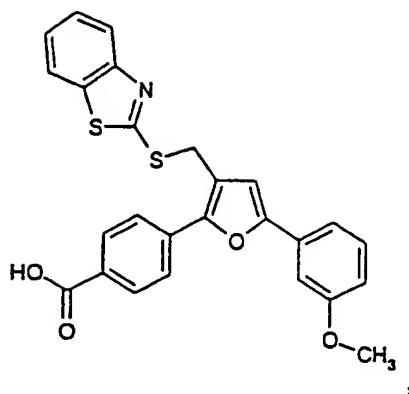
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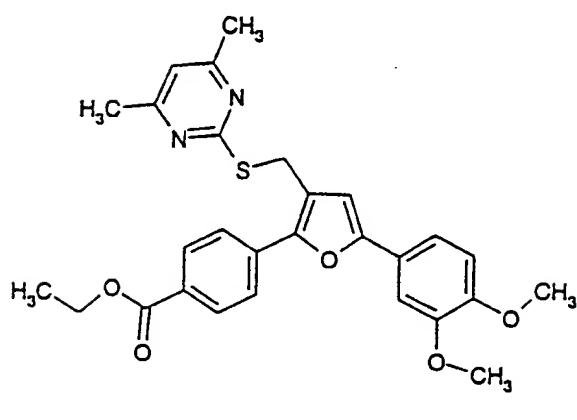
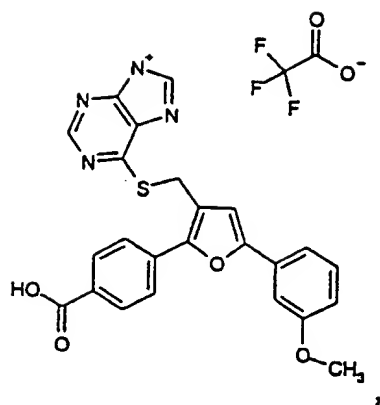




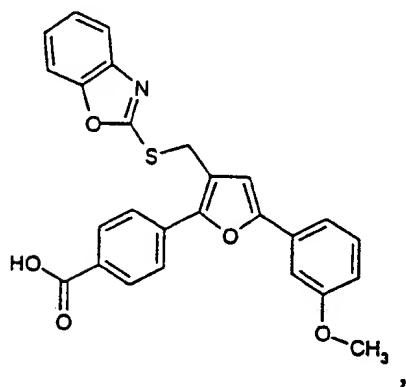


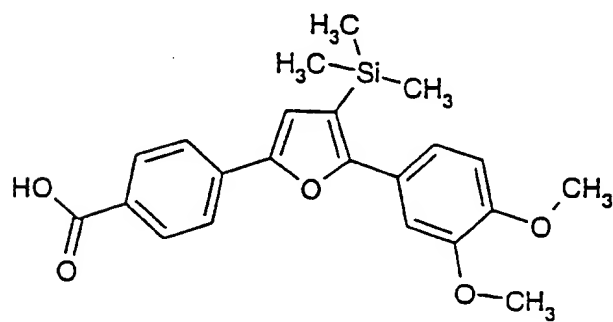
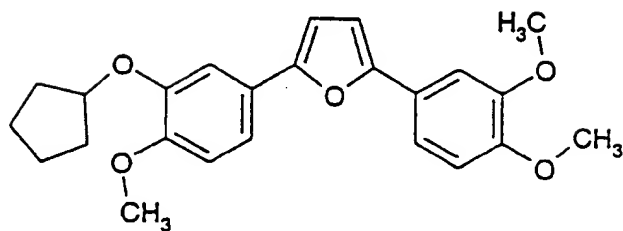
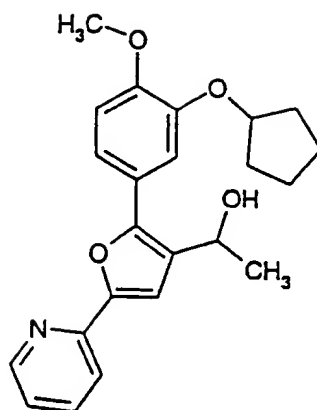




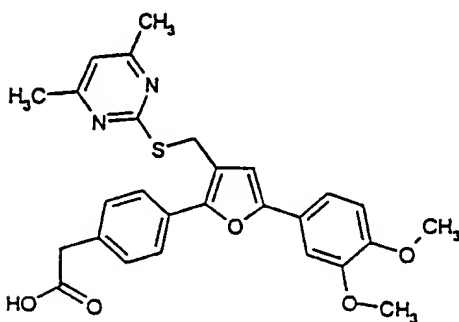


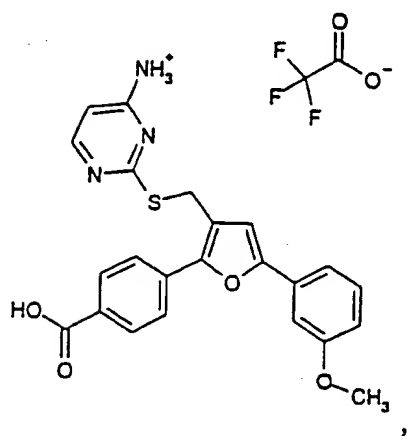
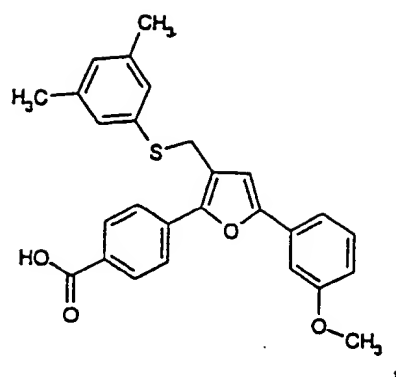
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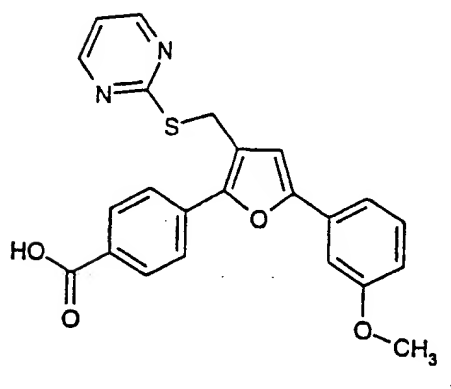


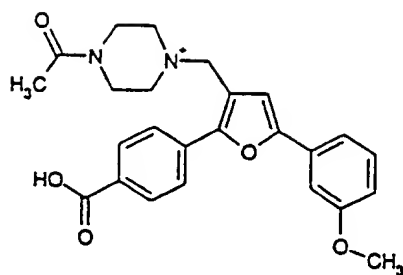
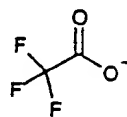
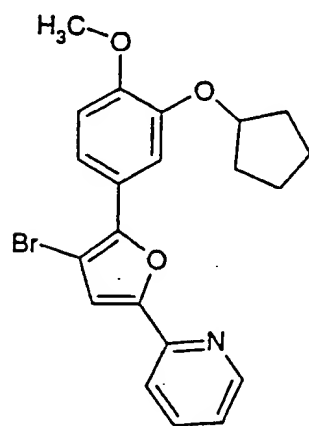
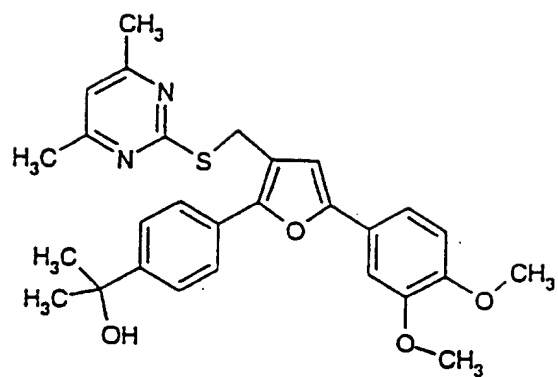
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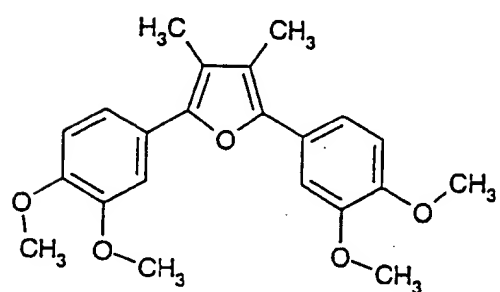
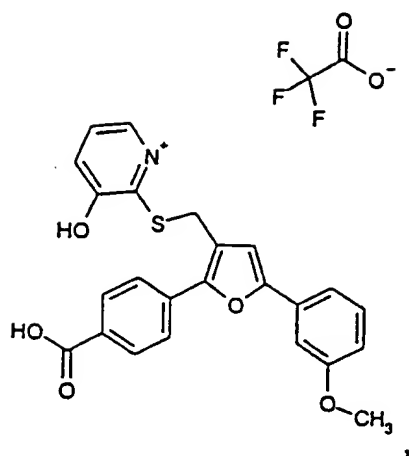




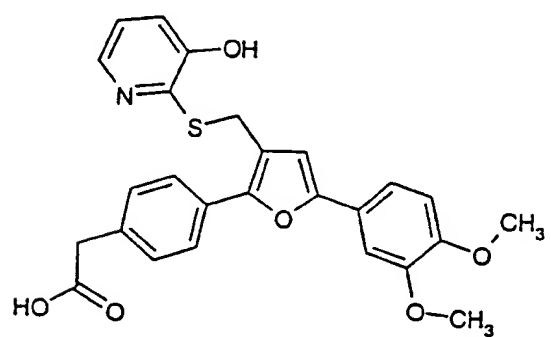
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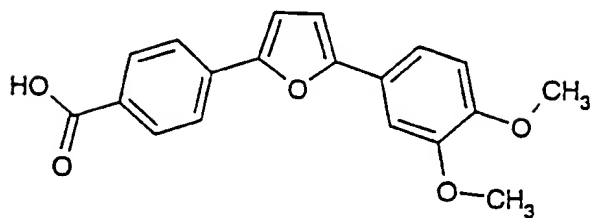
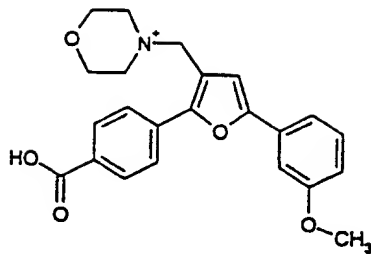
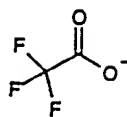




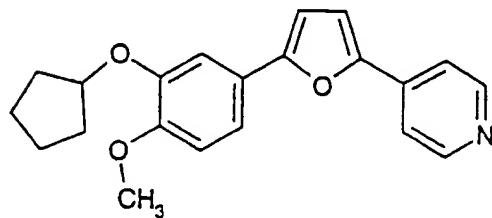
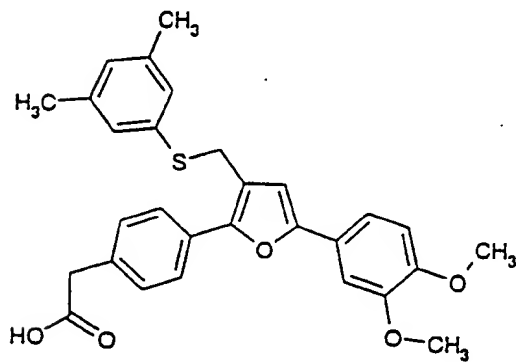


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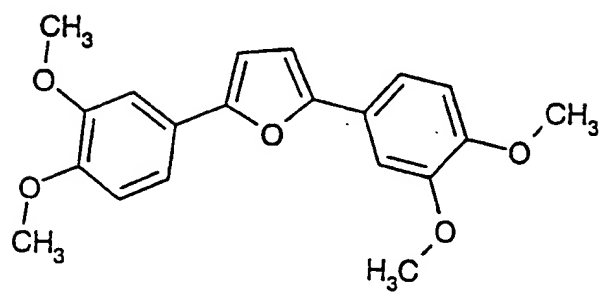
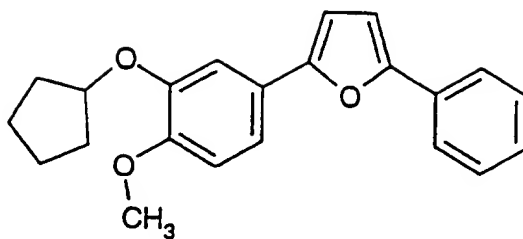




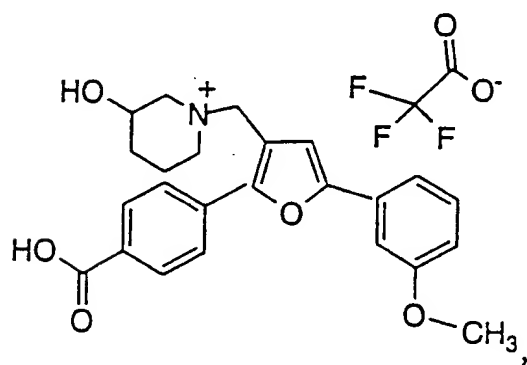
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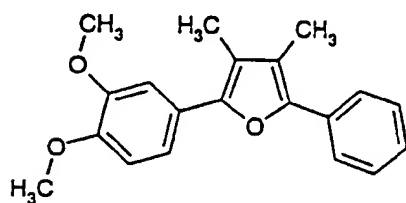
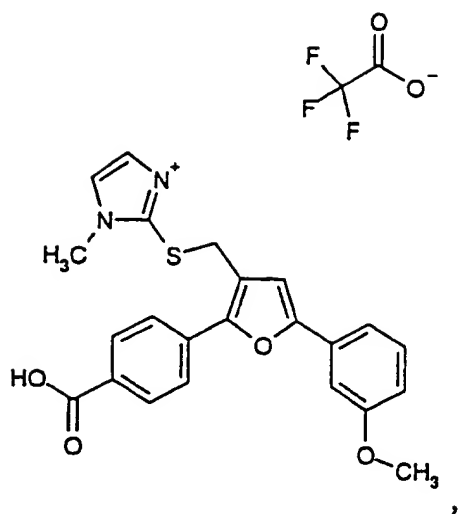
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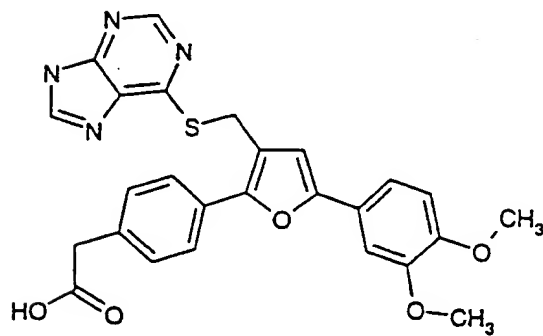
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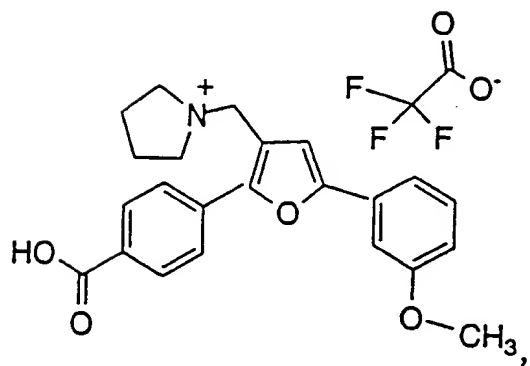
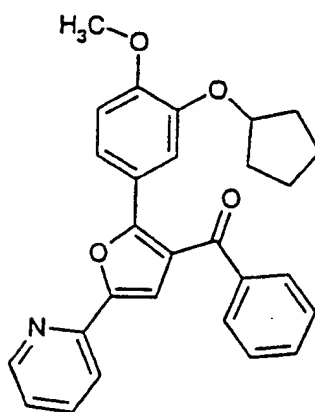
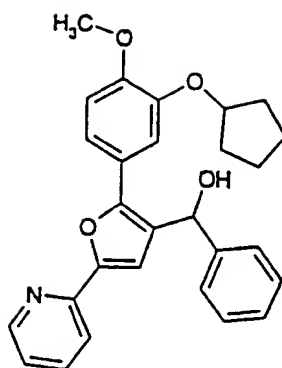




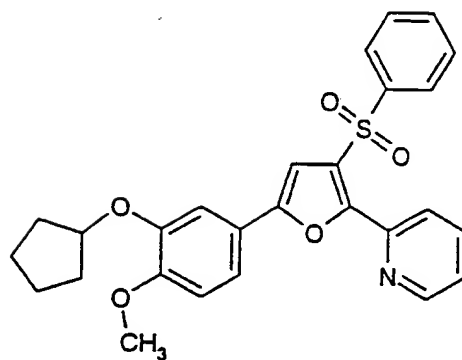
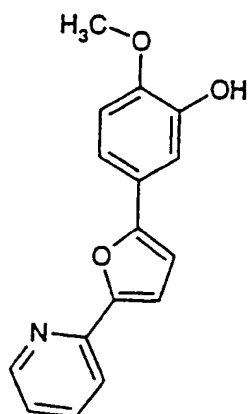
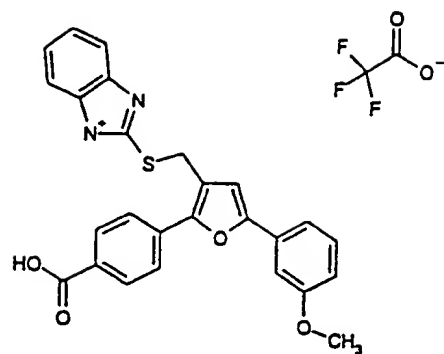


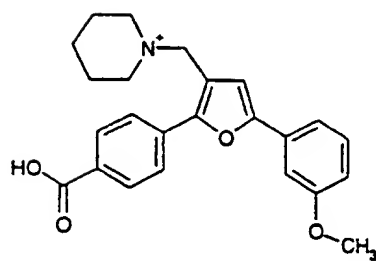
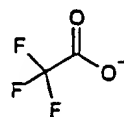
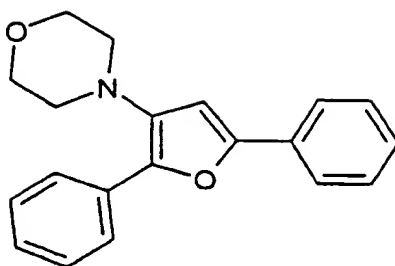
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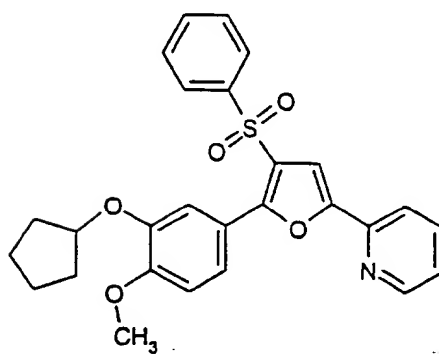


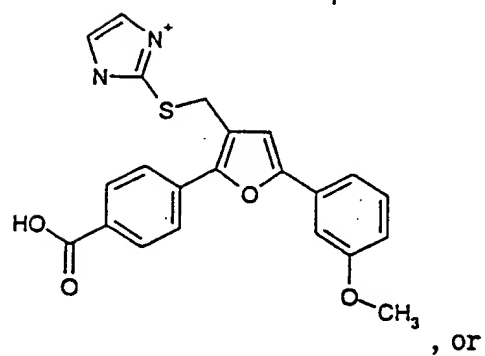
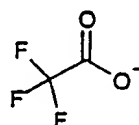
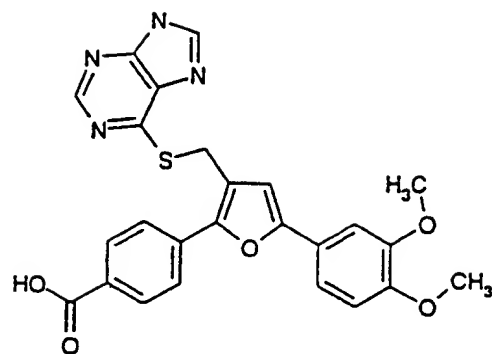
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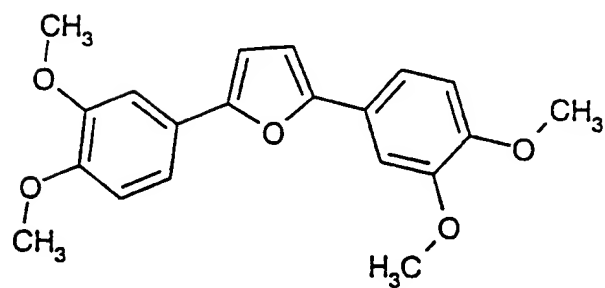


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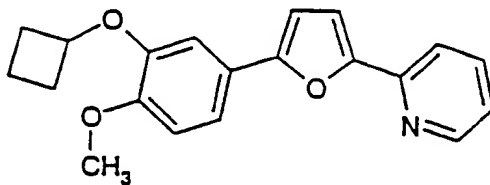
7. A pharmaceutical composition for treating asthma comprising a non-toxic therapeutically effective amount of a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.
- 5 8. A pharmaceutical composition for treating a phosphodiesterase IV mediated disease by increasing the cellular level of cAMP, comprising a non-toxic therapeutically effective amount of a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.
- 10 9. A method of treating asthma comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 15 10. A method of treating disease by inhibiting PDE IV comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to claim 1.
- 20 11. An anti-asthma pharmaceutical formulation comprising an acceptable, non-toxic, therapeutically effective amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5 or 6, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

12. A phosphodiesterase IV inhibitor pharmaceutical composition comprising an acceptable phosphodiesterase IV inhibiting amount, effective to increase the cellular level of cAMP, of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5 or 6, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.
13. A compound of formula (I), as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma.
14. Use of a compound of formula (I), as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating a phosphodiesterase IV mediated disease by increasing the cellular level of cAMP.
15. Use of a compound of formula (I), as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof as a phosphodiesterase IV inhibitor.

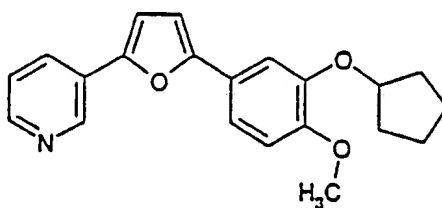
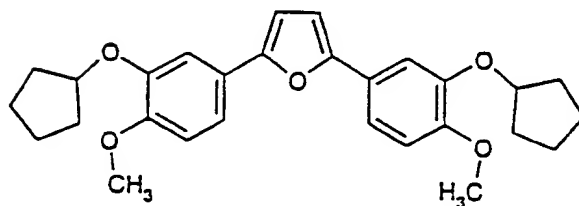
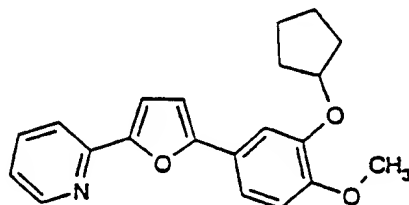
## AMENDED CLAIMS

[received by the International Bureau on 09 March 1999 (09.03.99);  
original claims 1-5 cancelled; claims 6-15 amended  
and renumbered as claims 1-10(19 pages)]

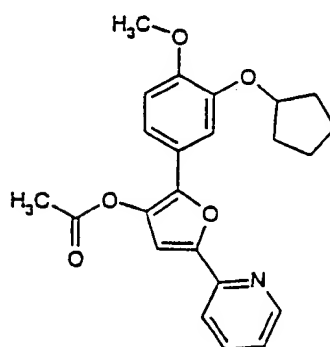
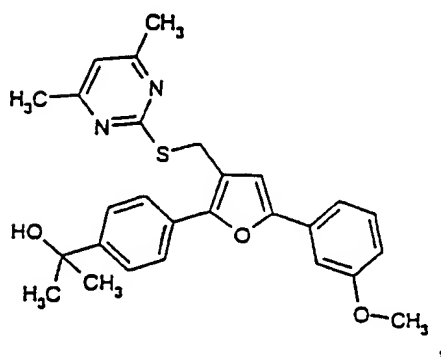
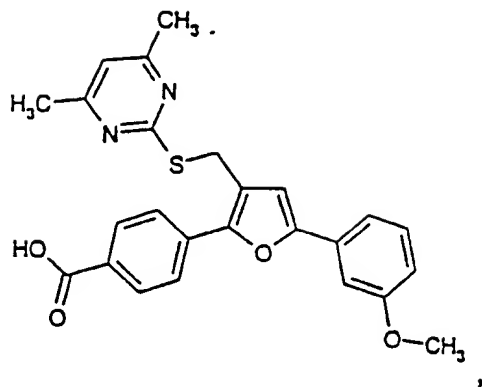
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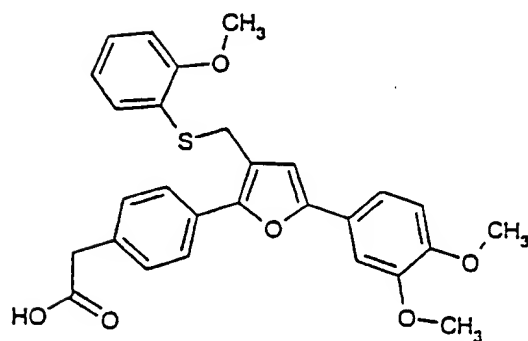
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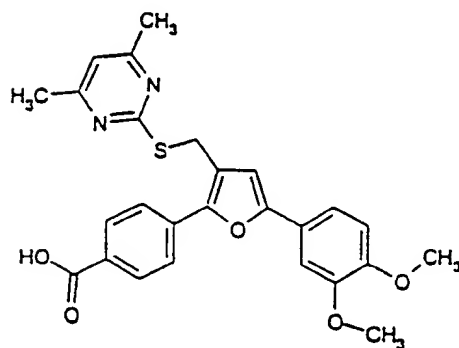
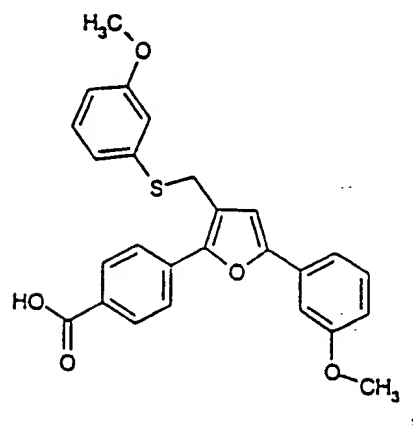
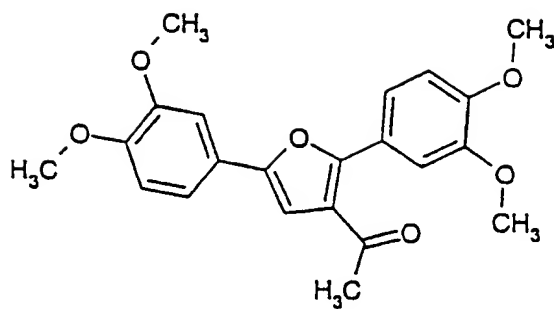


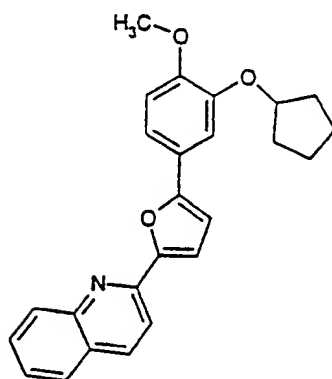
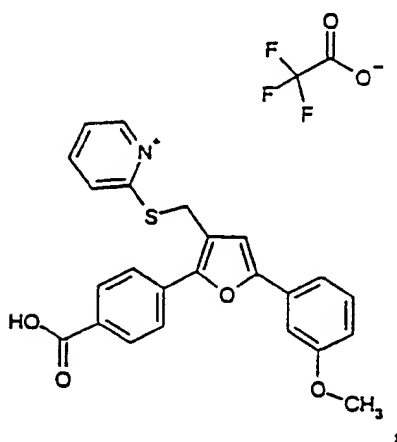
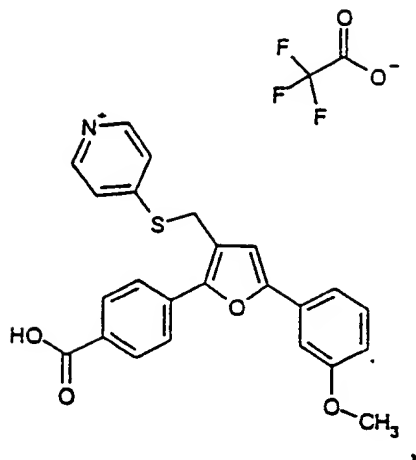


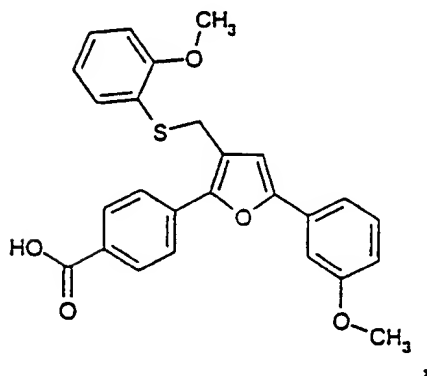
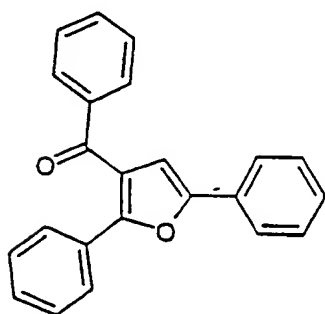
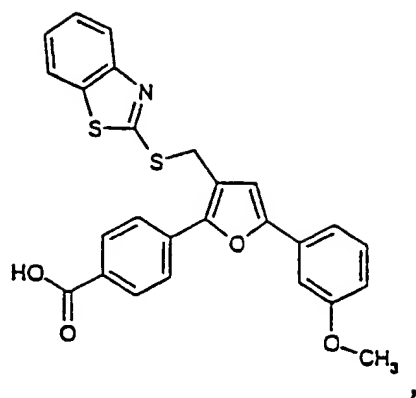


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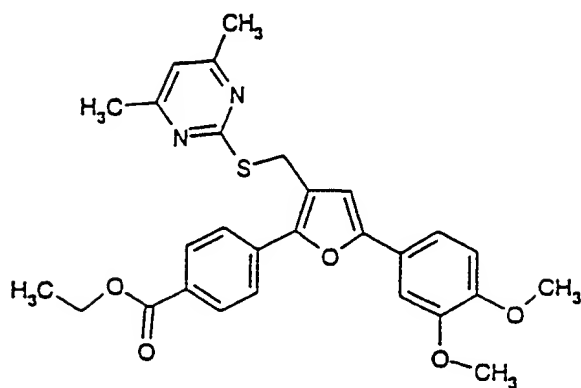
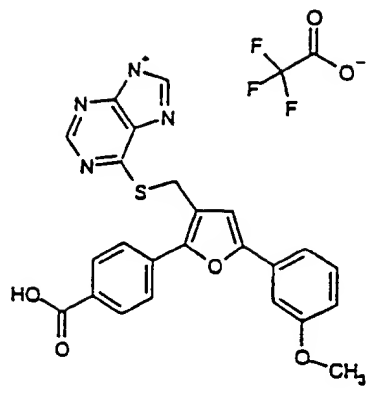




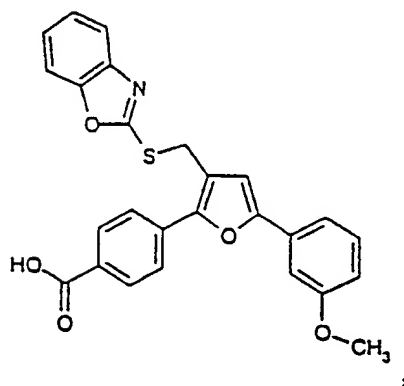


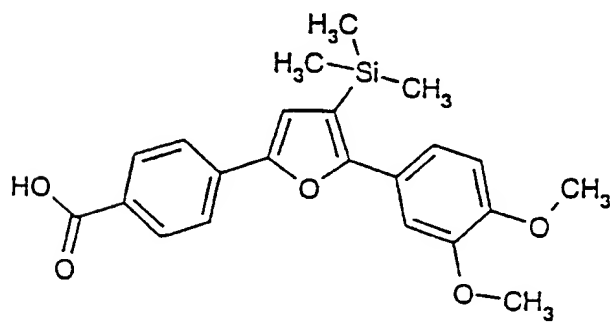
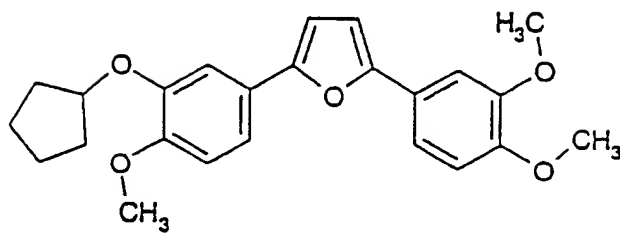
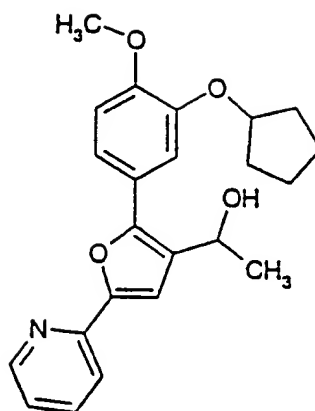


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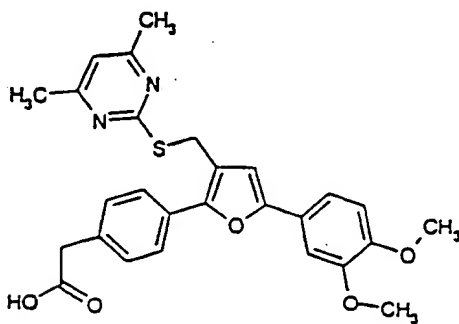


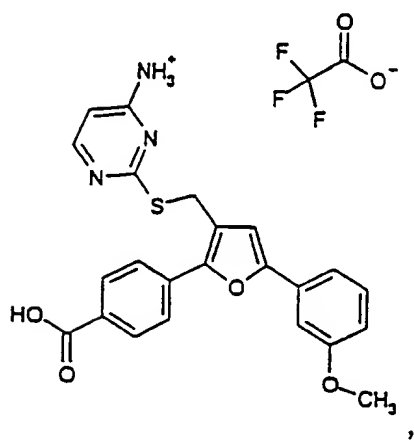
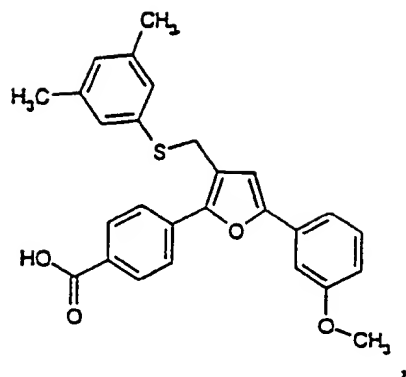
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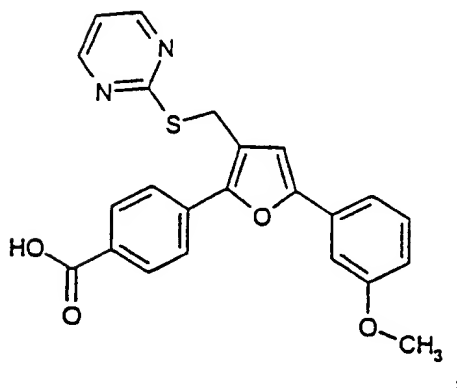


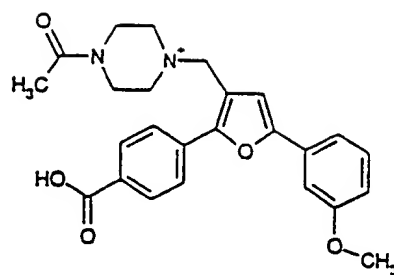
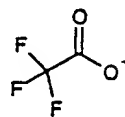
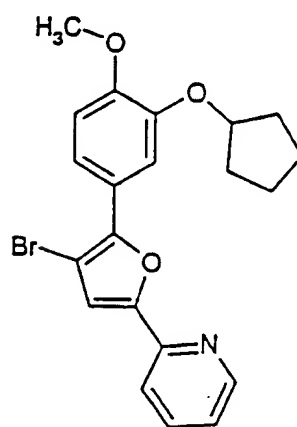
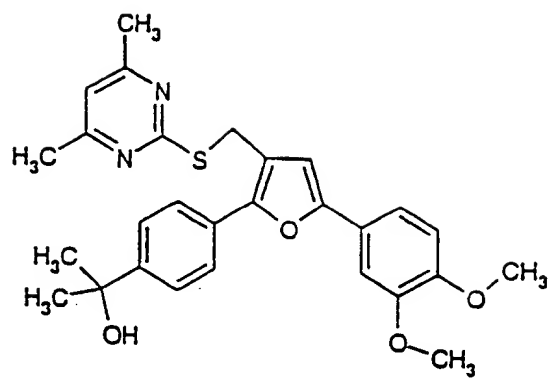
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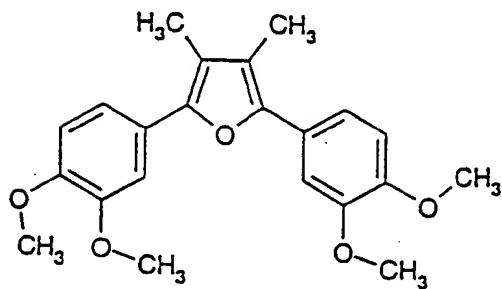
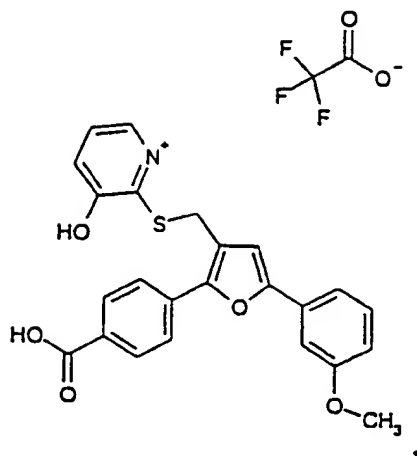


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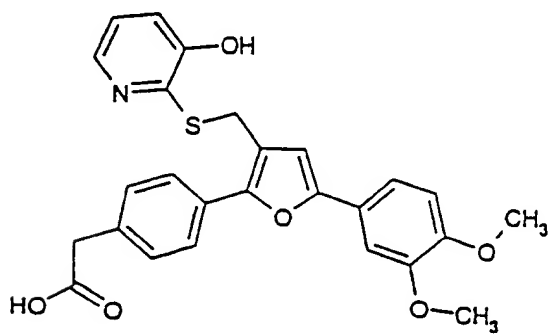


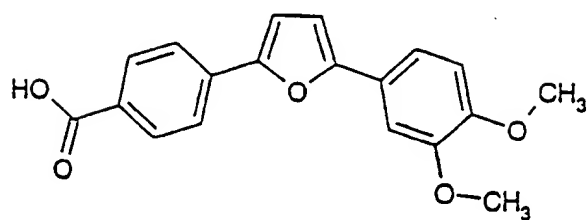
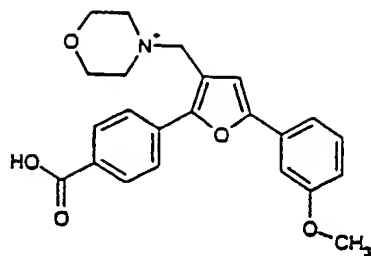
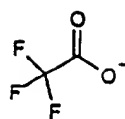




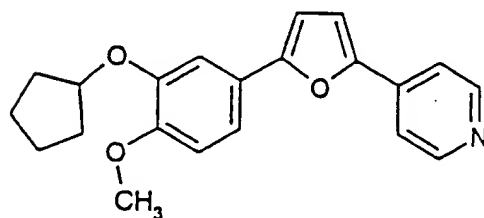
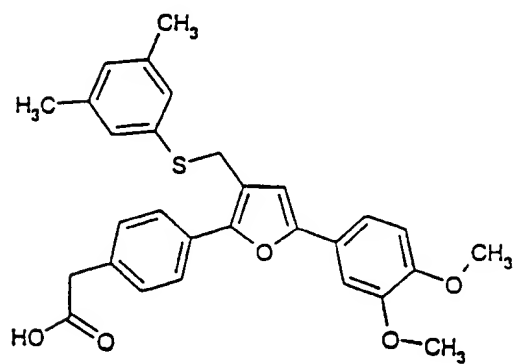


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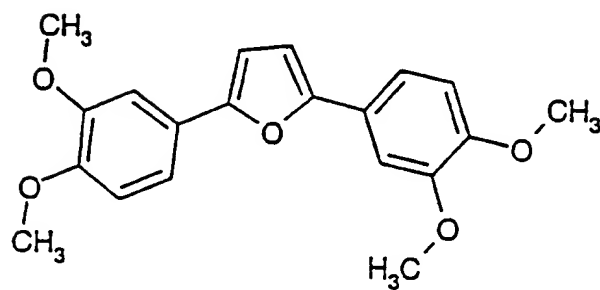
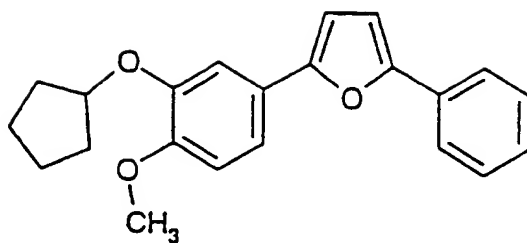




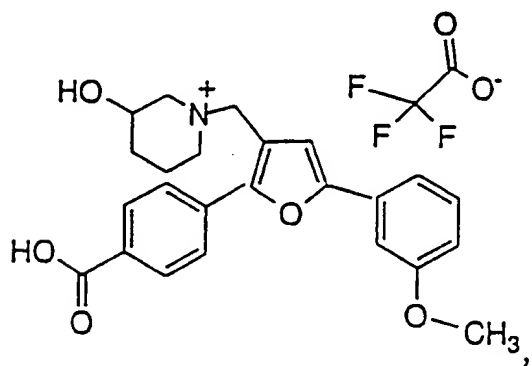
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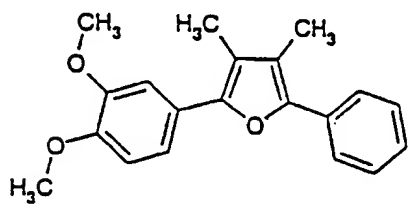
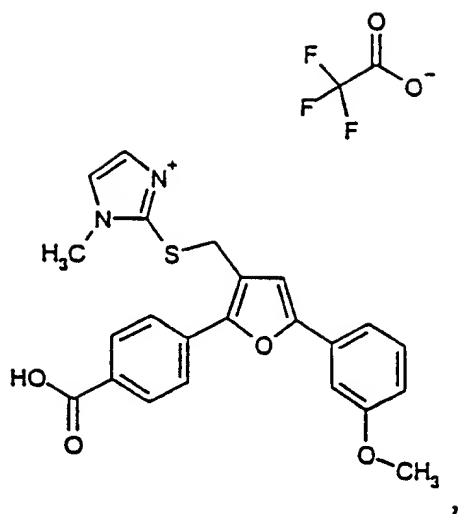


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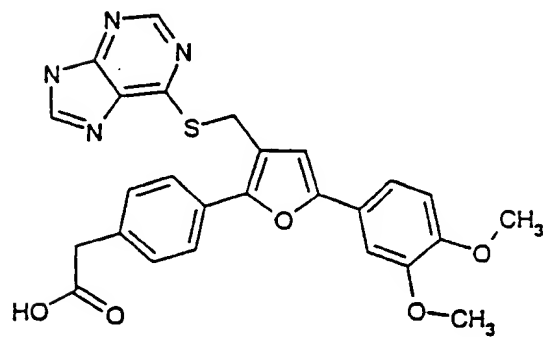


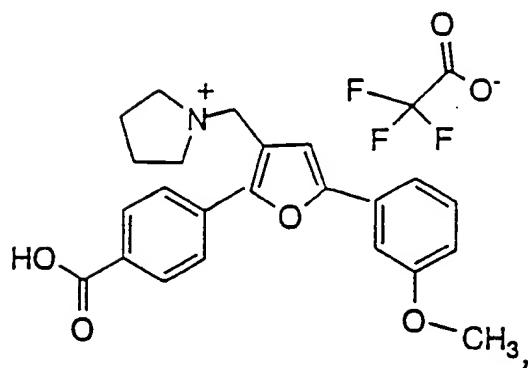
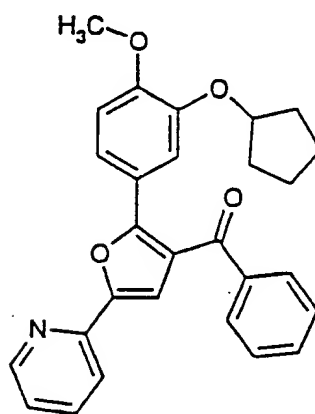
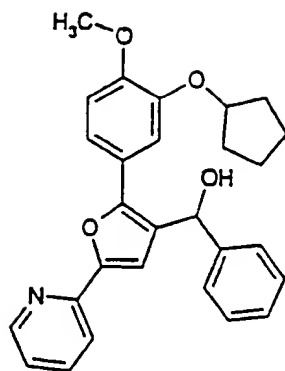
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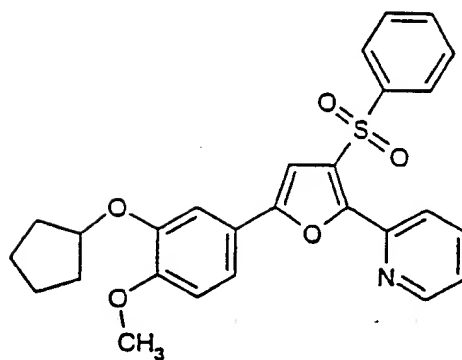
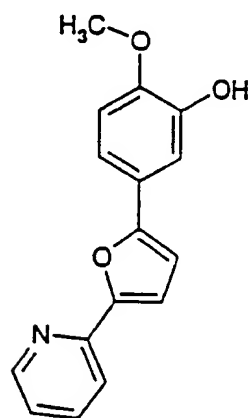
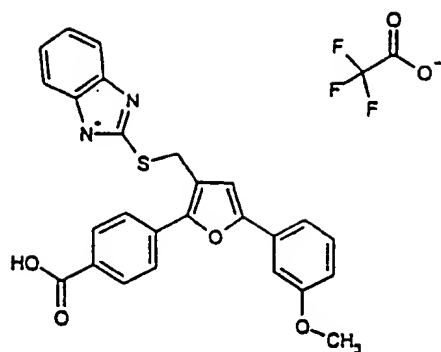




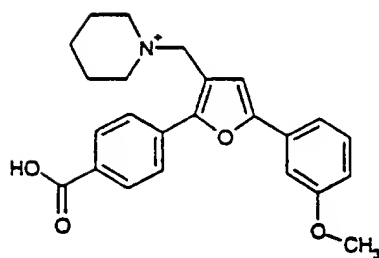
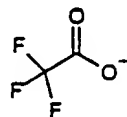
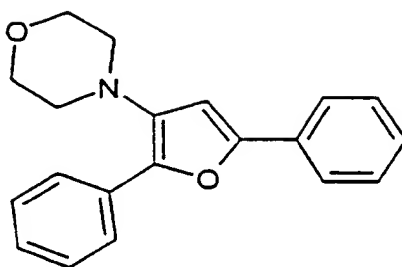
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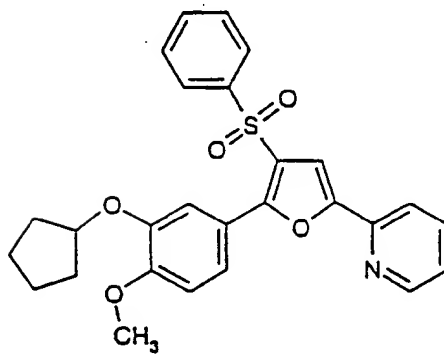


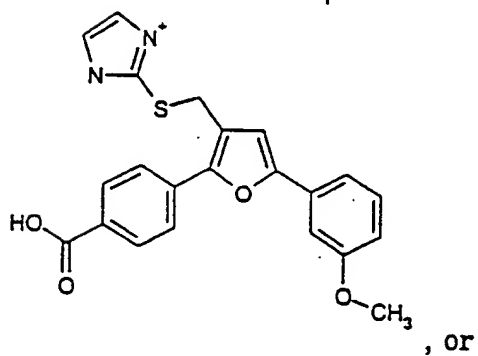
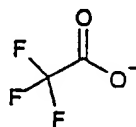
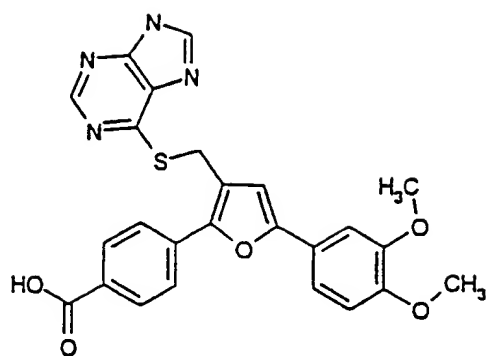


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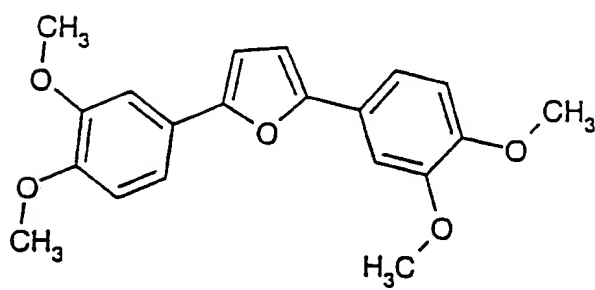


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2. A pharmaceutical composition for treating asthma comprising a non-toxic therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 5 3. A pharmaceutical composition for treating a phosphodiesterase IV mediated disease by increasing the cellular level of cAMP, comprising a non-toxic therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 10 4. A method of treating asthma comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 15 5. A method of treating disease by inhibiting PDE IV comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to claim 1.
- 20 6. An anti-asthma pharmaceutical formulation comprising an acceptable, non-toxic, therapeutically effective amount of a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

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7. A phosphodiesterase IV inhibitor pharmaceutical composition comprising an acceptable phosphodiesterase IV inhibiting amount, effective to increase the cellular level of cAMP, of a compound  
5 as defined in claim 1 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

8. A compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma.

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9. Use of a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating a phosphodiesterase IV mediated disease by increasing the cellular level of cAMP.

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10. Use of a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof as a phosphodiesterase IV inhibitor.

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b>					
IPC 6	C07D307/42	A61K31/34	C07D307/38	C07D307/46	C07D307/54
	C07D307/56	C07D307/64	C07D307/66	C07D473/38	C07D405/04
	C07D405/12	C07D417/12	C07D413/12	C07D405/06	C07F7/08
According to International Patent Classification (IPC) or to both national classification and IPC					
<b>B. FIELDS SEARCHED</b>					
Minimum documentation searched (classification system followed by classification symbols)					
IPC 6 C07D A61K C07F					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	EP 0 318 066 A (MERCK & CO INC) 31 May 1989 see claims and compound 24				1,2,7-15
X	CHEMICAL ABSTRACTS, vol. 114, no. 8, 25 February 1991 Columbus, Ohio, US; abstract no. 69042, WATANABE ET AL.: "Preparation of lignan compounds as ..." XP002088109 & JP-A-02180846 see abstract				1,5-15
-/--					
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>					
Date of the actual completion of the international search			Date of mailing of the international search report		
17 December 1998			13/01/1999		
Name and mailing address of the ISA			Authorized officer		
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Steendijk, M		

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. *
X	<p>DATABASE WPI  Section Ch, Week 9703  Derwent Publications Ltd., London, GB;  Class B03, AN 97-034276  XP002088115  &amp; WO 96 38412 A (TSUMURA &amp; CO)  , 5 December 1996  see abstract</p> <p>---</p>	1,2,5-8, 10-15
X	<p>DATABASE WPI  Section Ch, Week 9712  Derwent Publications Ltd., London, GB;  Class B03, AN 97-128649  XP002088116  &amp; JP 09 012457 A (TSUMURA &amp; CO)  , 14 January 1997  see abstract</p> <p>---</p>	1,5-8, 10-15
X	<p>DATABASE WPI  Section Ch, Week 9707  Derwent Publications Ltd., London, GB;  Class B03, AN 97-077348  XP002088117  &amp; WO 97 00068 A (TSUMURA &amp; CO)  , 3 January 1997  see abstract</p> <p>---</p>	1,2,5,7, 8,11-13
X	<p>EP 0 678 296 A (TSUMURA &amp; CO)  25 October 1995  see the whole document</p> <p>---</p>	1,2,5-8, 11-13
X	<p>US 4 595 693 A (BIFTU TESFAYE ET AL)  17 June 1986  see column 5 - column 6</p> <p>---</p>	1,2,5,6
X	<p>US 3 557 005 A (BROADDUS CHARLES D)  19 January 1971  see the whole document</p> <p>---</p>	1,2,5,6
X	<p>CHEMICAL ABSTRACTS, vol. 68, no. 19,  6 May 1968  Columbus, Ohio, US;  abstract no. 87079,  GUMP ET AL.: "Copper(I)substitutions.  Furans from ..."  XP002088110  &amp; J.Amer.Chem.Soc.,89(25),6770-6771 (1967)  see abstract</p> <p>---</p> <p style="text-align: center;">-/--</p>	1,2,5,6

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. 32
X	CHEMICAL ABSTRACTS, vol. 55, no. 5, 6 March 1961 Columbus, Ohio, US; TRAVERSO: "Intermediates necessary in the synthesis..." column 4468; XP002088111 & Gazz.chim.ital., 89, 1810-1817 (1959) see abstract ---	1,2,5,6
X	CHEMICAL ABSTRACTS, vol. 123, no. 7, 14 August 1995 Columbus, Ohio, US; abstract no. 83120, KUMAR ET AL.: "Synthesis of 3-alkoxy, 3-aryloxy and 3-substituted amino-2,5-diarylfurans ..." XP002088112 & Synth.Comm., 25(14), 2071-2078 (1995) see abstract ---	1,2,5,6
X	CHEMICAL ABSTRACTS, vol. 80, no. 23, 10 June 1974 Columbus, Ohio, US; abstract no. 133166, IYER ET AL.: "Potential antifertility agents..." XP002088113 & Indian J. Chem., 1973,11(12), 1260-1262 see abstract ---	1,2,5
X	US 3 531 497 A (YOUNGDALE GILBERT A) 29 September 1970 see the whole document ---	1,2,5
X	DATABASE WPI Section Ch, Week 8443 Derwent Publications Ltd., London, GB; Class B03, AN 84-265910 XP002088118 & JP 59 161390 A (KURARAY CO LTD) , 12 September 1984 see abstract ---	1,2
X	DATABASE WPI Section Ch, Week 9740 Derwent Publications Ltd., London, GB; Class E13, AN 97-431452 XP002088119 & JP 09 194471 A (MITSUBISHI CHEM CORP) , 29 July 1997 see abstract ---	1,2,5
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. 1-5
X	WATANABE ET AL.: "An efficient synthesis of 2(5H)-furanone and furan derivatives..." CHEM.PHARM.BULL., vol. 37, no. 11, 1989, pages 2914-2919, XP002088108 see page 2917 -----	1,2,5
X	DAS B P ET AL: "SYNTHESIS AND ANTIPROTOZOAL ACTIVITY OF 2,5-BIS(4-GUANYLPHENYL) FURANS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 20, no. 4, April 1977, pages 531-536, XP000605199 see page 532 -----	1,2,5
X	CHEMICAL ABSTRACTS, vol. 65, no. 11, 21 November 1966 Columbus, Ohio, US; AUTERHOFF ET AL.: "Guaiac resins..." column 16925; XP002088114 & Arch.Pharm., 299(7), 618-626 (1966) see abstract -----	1,5

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EP 0318066	A	31-05-1989	DE 3873278 A JP 1186881 A US 4999436 A	03-09-1992 26-07-1989 12-03-1991
EP 0678296	A	25-10-1995	AU 6955394 A US 5629340 A CA 2153686 A WO 9415594 A	15-08-1994 13-05-1997 21-07-1994 21-07-1994
US 4595693	A	17-06-1986	NONE	
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